Regio- and Stereoselective Reactions of 17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester

Charlotta Liljebris,[†,‡] Björn M. Nilsson,[‡] Bahram Resul,[‡] and Uli Hacksell*[,†]

Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Box 574, Uppsala University, S-751 23 Uppsala, Sweden and Pharmacia AB, S-751 82 Uppsala, Sweden

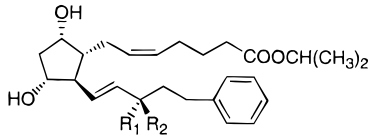
Received January 17, 1996[⊗]

Novel prostaglandin $F_{2\alpha}$ derivatives, functionalized at C13 and C14, have been prepared. 17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropyl ester [(15*S*)-**1**] and its epimer [(15*R*)-**1**] were stereoselectively epoxidized, using Sharpless conditions, to produce each of the four diastereomeric epoxides (15*S*)-**2**, (15*S*)-**3**, (15*R*)-**2**, and (15*R*)-**3**. Treatment of the four epoxides with LiOH stereospecifically-produced the pentahydroxy substituted analogues **12** and **13**. Alternatively, epoxides **2** and **3** were allowed to react with thiophenolate ion. The attack of the sulfur nucleophile on the epoxide occurred at either C13 or C14 depending on the stereochemistry of the epoxide and of C15.

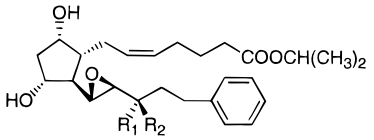
Introduction

Ongoing studies in our laboratories focus on exploring the relation between antiglaucoma activity and the structure of the ω-chain of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) isopropyl ester analogues.[1,2] Previously, we have reported the synthesis of phenyl-substituted analogues of the 15*S* and 15*R* epimers of 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ isopropyl ester [(15*S*)-**1** and (15*R*)-**1**, respectively].[3,4] In the present study, we have focused our attention to the allylic function of the ω-chain since functionalization of the allylic alcohol moiety would allow for expansion of the structural diversity of this class of molecules using a single and minimally protected key-intermediate.

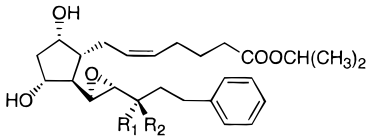
The asymmetric Sharpless epoxidation reaction[5] provided a convenient method for stereoselectively converting (15*S*)-**1** and (15*R*)-**1** to the diastereomeric epoxy alcohols (15*S*)-**2**, (15*R*)-**2**, (15*S*)-**3**, and (15*R*)-**3**. We have also studied regioselective ring-opening reactions of the epoxy alcohols using sulfur and oxygen nucleophiles, such as thiophenolate and hydroxide anions. Most of these reactions provide isomerically pure compounds in acceptable yields.



(15*S*)-**1**: R_1 = OH, R_2 = H
(15*R*)-**1**: R_1 = H, R_2 = OH



(15*S*)-**2**: R_1 = OH, R_2 = H
(15*R*)-**2**: R_1 = H, R_2 = OH



(15*S*)-**3**: R_1 = OH, R_2 = H
(15*R*)-**3**: R_1 = H, R_2 = OH

Results and Discussion

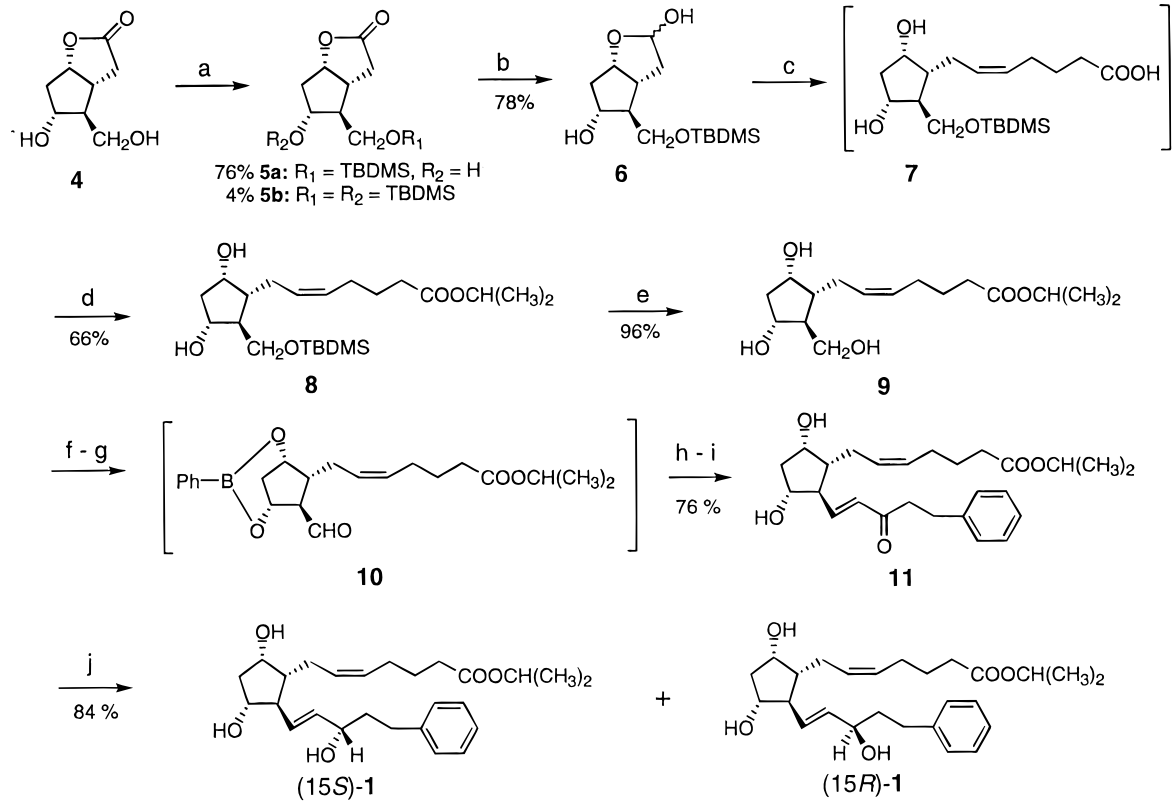
Synthesis of (15*S*)-1 and (15*R*)-1. These compounds were prepared by a slightly different strategy than that described by us previously,[1−4] and the present method also represents a modified version of Corey's general method (Scheme 1);[6] treatment of the Corey lactone **4** with *tert*-butyldimethylchlorosilane afforded a mixture of mono- and disilylated products (**5a** and **5b**) that were separated by column chromatography. Reduction of the lactone function of **5a** using DIBAL-H[7] afforded the lactol **6**. Wittig reaction with (4-carboxybutyl)triphenylphosphonium bromide[8] afforded the acid **7** as a 95:5 mixture of *cis* and *trans* isomers. Compound **7** was esterified with 2-iodopropane and K_2CO_3 to give **8** in 66% overall yield from **6**. Compound **8** was deprotected using $NaHSO_4 \cdot H_2O$, affording triol **9** in 96% yield. The triol **9** was C9 and C11 hydroxyl diprotected *in situ* using phenylboronic acid[9] and was then oxidized with pyridinium chlorochromate (PCC)/Al_2O_3[10] to aldehyde **10** which was not isolated

[†] Uppsala University.
[‡] Pharmacia AB.
[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1996.

(1) Resul, B.; Stjernschantz, J.; No, K.; Liljebris, C.; Selén, G.; Astin, M.; Karlsson, M.; Bito, L. Z. *J. Med. Chem.* **1993**, *36*, 243−248; **1993**, *36*, 2242.
(2) Stjernschantz, J.; Resul, B. *Drugs Future* **1992**, *17*, 691−704.
(3) Liljebris, C.; Resul, B.; Hacksell, U. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 241−244.
(4) Liljebris, C.; Selén, G.; Resul, B.; Stjernschantz, J.; Hacksell, U. *J. Med. Chem.* **1995**, *38*, 289−304.
(5) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (c) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, Chapter 3.2. (d) Smith, J. G. *Synthesis* **1984**, 629−656. (e) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 7, pp 193−245. (f) Pfenniger, A. *Synthesis* **1986**, 89−116. (g) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8, p 247.
(6) (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675−5677. (b) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397−398.
(7) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213−214.
(8) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

S0022-3263(96)00098-9 CCC: $12.00

Scheme 1[a]



[a]Reagents: (a) TBDMSCl, Et_3N, DMAP/CH_2Cl_2; (b) DIBAL/THF, -78 °C; (c) KOtBu, $BrPh_3P(CH_2)_4COOH$/THF, -30 °C; (d) K_2CO_3, $ICH(CH_3)_2/CH_3CN$; (e) $NaHSO_4 \cdot H_2O$/THF-H_2O; (f) $PhB(OH)_2/CH_2Cl_2$; (g) PCC, Al_2O_3/CH_2Cl_2; (h) LiCl, $(CH_3O)_2POCH_2CO(CH_2)_2C_6H_5$, DIPEA/$CH_3CN$, -15 °C → r.t. ; (i) H_2O_2/THF; (j) $NaBH_4$, $CeCl_3 \cdot 7H_2O$.

but condensed with dimethyl (2-oxo-4-phenylbutyl)phosphonate[2] under Horner−Wadsworth−Emmons conditions.[11] Deprotection with H_2O_2 furnished ketone **11** in 76% overall yield from **9**. Nonstereoselective reduction of **11** using sodium borohydride in the presence of cerium chloride heptahydrate[12] provided an epimeric mixture of (15*S*)-**1** and (15*R*)-**1**. The isomers were readily separated by column chromatography to provide isomerically pure (15*S*)-**1** and (15*R*)-**1** in 38% and 46% yield, respectively. Alternatively, the reduction of **11** could be performed in a stereoselective manner using lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride (*S*-Alpine hydride)[13] to provide predominantly the 15*S*-epimer (44% de).

Epoxidation Reactions of (15*S*)-1 and (15*R*)-1. Asymmetric epoxidation of the borate ester of (15*S*)-**1** by the Sharpless method[5] using (+)-L-diisopropyl tartrate [(+)-DIPT] gave 93% de[14] of the β-epoxide (15*S*)-**2** in 66% yield (Scheme 2). Attempts to epoxidize unprotected **1** were unsuccessful. Purification by preparative HPLC afforded isomerically pure (15*S*)-**2**. The reaction was complete after 10 min at 0 °C and 2 h at ambient temperature. Attempts to increase the % de by running the reaction at lower temperatures were not successful. Epoxidation of the slow-reacting isomer (15*R*)-**1**, using (+)-DIPT, gave a diastereomeric mixture of (15*R*)-**2** and (15*R*)-**3** (β- and α-epoxide, respectively) in a total yield of 60%; the epoxidation gave 22% de of the β-epoxide (15*R*)-**2** (Scheme 2). The reaction was complete after 12 h at 0 °C and 4 h at ambient temperature, which gave an optimal % de. Separation of the mixture by preparative HPLC afforded isomerically pure (15*R*)-**2** (21%) and isomerically pure (15*R*)-**3** (19%).

Sharpless epoxidation using (−)-DIPT gave the opposite results. The fast-reacting isomer (15*R*)-**1** gave 92% de of the α-epoxide (15*R*)-**3** in 76% yield (Scheme 2). Purification by preparative HPLC afforded isomerically pure (15*R*)-**3**. Epoxidation of the slow-reacting isomer (15*S*)-**1** using (−)-DIPT produced a diastereomeric mixture of (15*S*)-**2** and (15*S*)-**3** with 62% de of the α-epoxide (15*S*)-**3** (Scheme 2). Purification by preparative HPLC afforded isomerically pure (15*S*)-**3** (44%).

Ring-Opening Reactions. Nucleophilic ring-opening of the borate protected isomeric epoxides with LiOH proceeded smoothly. Reaction of (15*S*)-**2** with LiOH afforded isomerically pure (15*S*)-**12** (Scheme 2). The proposed stereochemistry is based on nucleophilic attack at C13. In neutral and basic conditions nucleophilic ring-opening of epoxides occur by a S_N2 mechanism at the least sterically hindered carbon, but also electronic factors play an important role. Electronically, a substituent may exert its effect through resonance or induction or both. An electron-withdrawing substituent dis-

(9) (a) Nishizawa, E. E.; Miller, W. L.; Gorman, R. R.; Bundy, G. L. *Prostaglandins* **1975**, *9*, 109−120. (b) Ferrier, R. J.; Prasad, D.; Rudowski, A.; Sangster, I. *J. Chem. Soc.* **1964**, 3330−3334.

(10) Cheng, Y.-S.; Liu, W.-L.; Chen, S. *Synthesis* **1980**, 223−224.

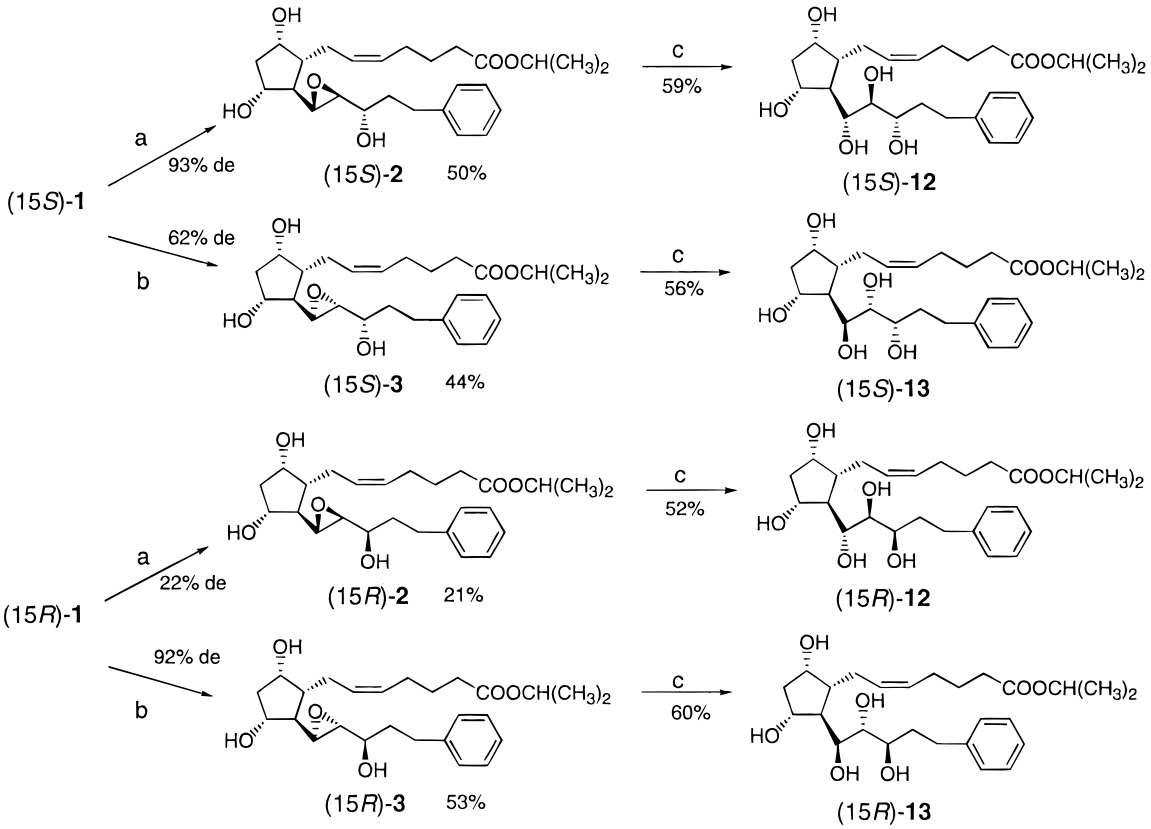
(11) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(12) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

(13) (a) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534−2536. (b) Ramachandran, P. V.; Brown, H. C.; Swaminathan, S. *Tetrahedron: Asymmetry* **1990**, *1*, 433−436.

(14) This is in agreement with the predicted stereoselectivity of secondary allylic alcohols, see ref 5.

Scheme 2[a]



[a]Reagents: (a) (1) $PhB(OH)_2/CH_2Cl_2$; (2) (+)-DIPT, $Ti(OiPr)_4$, TBHP/CH_2Cl_2; (3) H_2O_2/THF; (b) (1) $PhB(OH)_2/CH_2Cl_2$; (2) (-)-DIPT, $Ti(OiPr)_4$, TBHP/CH_2Cl_2; (3) H_2O_2/THF; (c) (1) $PhB(OH)_2$/THF; (2) LiOH, 80 °C; (3) H_2O_2/THF.

Table 1. Vicinal Coupling Constants Used for Stereochemical Assignment[a]

compound	$J_{12,13}$	$J_{13,14}$	$J_{14,15}$
(15*S*)-**12**	3.6	8.6	1.6
(15*S*)-**13**	2.0	7.0	6.7
(15*R*)-**12**	3.3	8.5	5.5
(15*R*)-**13**	2.1	7.9	2.5

[a] Values are given in Hz.

couraged ring-opening at the proximal carbon atom.[15] Based on the assumption that electronic factors dominate, the electron withdrawing inductive effect of the C15-OH should direct nucleophilic ring-opening to the distal carbon atom. Nucleophilic ring-opening of (15*S*)-**3**, (15*R*)-**2**, and (15*R*)-**3** with LiOH gave (15*S*)-**13**, (15*R*)-**12**, and (15*R*)-**13**, respectively, with similar regioselectivities and yields (Scheme 2). The reactions were monitored by analytical HPLC, and although some negligible additional peaks could be detected, no other products could be isolated.

The stereochemical assignments of the pentols are supported by the NMR spectroscopic data. However, the structural assignments for **12** and **13** are yet to be determined with absolute certainty. In (15*S*)-**12** and (15*R*)-**12**, where the C13-OH is α-positioned, the vicinal coupling constants between C12-H and C13-H have the same magnitude (Table 1). In addition, the $J_{12,13}$ couplings in (15*S*)-**13** and (15*R*)-**13**, where the C13-OH is *β*-positioned, are comparable. On the other hand, the $J_{14,15}$ couplings in (15*S*)-**13** and (15*R*)-**12**, where the C14-OH and C15-OH have *cis* relationship, are of the same magnitude. In (15*S*)-**12** and (15*R*)-**13**, where the C14-OH and C15-OH have *trans* relationship, the $J_{14,15}$ couplings are smaller (Table 1). The assignment of the configuration at C15 is based on the assumption that the stereochemistry of the starting materials is retained in the products.

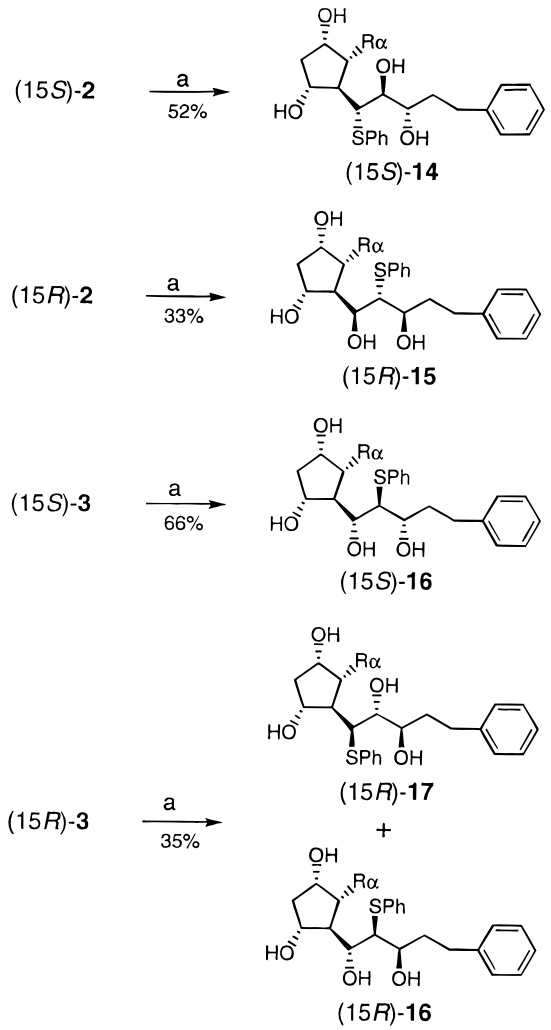
When sodium thiophenolate was used as a nucleophile, the ring-openings of the four borate protected epoxide isomers proceeded with different regioselectivities (Scheme 3). Reaction of (15*S*)-**2** with thiophenolate produced sulfide (15*S*)-**14**, the thiolate ion attacking at C13. In contrast, epoxides (15*R*)-**2** and (15*S*)-**3** were ring-opened by attack at C14 producing sulfides (15*R*)-**15** and (15*S*)-**16**, respectively. Epoxide (15*R*)-**3**, on the other hand, produced a 69:31 mixture of C13 and C14 ring-opened products, (15*R*)-**17** and (15*R*)-**16**, respectively, in 35% overall yield. Column chromatographic separation gave isomerically pure (15*R*)-**17** (14%) and (15*R*)-**16**(11%).

The stereochemical assignments of the sulfides where based on NMR spectroscopic data and the mechanistic assumption that ring opening occurred by a S_N2 mechanism. The ^{13}C NMR chemical shifts of C13 and C14 bearing a phenylthio group occur upfield (51−59 ppm) of carbons bearing a hydroxyl group (73−77 ppm) (Table 2).

In conclusion, epoxides **2** and **3** may serve as readily accessible key intermediates in the synthesis of novel $PGF_{2\alpha}$ derivatives substituted with various groups at C13 and C14.

(15) (a) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67−79. (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696−5704.

Scheme 3[a]



[a]Reagents: (a) (1) $PhB(OH)_2$/THF; (2) PhSNa/EtOH, 45 °C; (3) H_2O_2.

Table 2. ^{13}C NMR Chemical Shift Values Used for Regiochemical Assignment[a]

compound	C11	C12	C13	C14	C15
(15*S*)-**14**	73.2	51.2	52.8	77.1	71.9
(15*R*)-**15**	77.4	56.1	76.0	59.4	71.5
(15*S*)-**16**	73.9	56.0	72.9	59.5	72.7
(15*R*)-**17**	79.4	52.1	55.3	76.2	71.7
(15*R*)-**16**	74.0	55.9	72.4	59.0	71.7

[a] Values are given as ppm referenced to internal TMS.

Experimental Section[4]

Preparative HPLC was performed using a silica gel column (21.4 × 250 mm); mobile phase: 3−7% of ethanol in isohexane; flow rate: 13 mL/min, unless otherwise noted; detection: 220 nm. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden, or by Analytische Laboratorien, Gummersbach, Germany, and were within 0.4% of the calculated values.

(1*S*,5*R*,6*R*,7*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-7-hydroxy-2-oxabicyclo[3.3.0]octane-3-one (5a) and (1*S*,5*R*,6*R*,7*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-7-[(*tert*-butyldimethylsilyl)oxy]-2-oxabicyclo[3.3.0]octane-3-one (5b). Triethylamine (4.28 g, 42.3 mmol) and 4-(dimethylamino)pyridine (533 mg, 4.36 mmol) were added to a stirred suspension of the Corey lactone[6] (1*S*,5*R*,6*R*,7*R*)-6-(hydroxymethyl)-7-hydroxy-2-oxabicyclo[3.3.0]octane-3-one (**4**; 7.51 g, 43.6 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was temporarily cooled to −20 °C on a dry ice bath and *t*$BuMe_2$SiCl (6.44 g, 42.7 mmol) in CH_2Cl_2 (60 mL) was added. The ice bath was removed after 1.5 h, and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated in vacuo. Ether was added, and the triethylammonium hydrochloride salt was filtered off. Concentration of the filtrate in vacuo afforded the crude product as an oil, which was purified by column chromatography using EtOAc/*n*-hexane (1:1) as eluent. First eluted was the disilylated lactone **5b**. Further elution gave 9.15 g (76%) of pure monosilylated lactone **5a** as a white solid. The obtained disilylated **5b** was contaminated with *t*$BuMe_2$SiCl. However, a second column on impure **5b** using *n*-hexane/ether (3:2) as eluent gave 577 mg (4%) of pure **5b** as a white solid.

5a: TLC R_f = 0.40 [*n*-hexane/EtOAc (1:1)]; mp 60.5−62 °C, lit.[16] 61−62.5 °C; $[\alpha]_D$ −22.7 (*c* 1.21, CH_3CN), −15.3 (*c* 1.05, $CHCl_3$), lit.[16] −14.1 ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.06 [6H, s, $Si(CH_3)_2$], 0.89 [9H, s, $C(CH_3)_3$], 1.94−2.04 (2H, m, H_6 and $H_{8'}$), 2.42 (1H, ddd, $H_{8''}$, J = 6.7, 6.7, 15.0), 2.50−2.54 (2H, m, $H_{4\beta}$ and C7-OH), 2.62 (1H, m, H_5), 2.78 (1H, dd, $H_{4\alpha}$, J = 10.1, 18.0), 3.60 (1H, dd, CH_2OSi, J = 6.4, 10.1), 3.69 (1H, dd, CH_2-OSi, J = 5.2, 10.1), 4.12 (1H, m, H_7), 4.91 (m, 1H, H_1). Anal. Calcd for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15. Found: C, 58.8; H, 9.15.

5b: TLC R_f = 0.53 [*n*-hexane/ether (1:1)]; mp 104.5−105.5 °C; $[\alpha]_D$ −26.3 (*c* 1.03, CH_3CN); ^{1}H NMR ($CDCl_3$) δ 0.04 (6H, two peaks, $Si(CH_3)_2'$), 0.05 (6H, two peaks, $Si(CH_3)_2''$), 0.87 (9H, s, $C(CH_3)_3'$), 0.89 (9H, s, $C(CH_3)_3''$), 1.94−2.01 (2H, m, H_6 and $H_{8'}$), 2.23 (1H, ddd, $H_{8''}$, J = 5.8, 6.9, 14.7), 2.53 (2H, dd, $H_{4\beta}$, J = 3, 18), 2.67 (1H, m, H_5), 2.77 (1H, dd, $H_{4\alpha}$, J = 10.7, 17.8), 3.48 (1H, dd, CH_2OSi, J = 5.8, 10.2), 3.55 (1H, dd, CH_2OSi, J = 5.2, 10.4), 4.12 (1H, m, H_7), 4.92 (m, 1H, H_1). Anal. Calcd for $C_{20}H_{40}O_4Si_2$: C, 59.95; H, 10.06. Found: C, 59.9; H, 10.2.

(1*S*,5*R*,6*R*,7*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-7-hydroxy-2-oxabicyclo[3.3.0]octane-3-ol (6). Diisobutylaluminum hydride (DIBAL-H, 20 wt % in toluene, 65 mL, 79.1 mmol) was added dropwise during 30 min to a stirred solution of lactone **5a** (8.96 g, 31.3 mmol) in a 1:1 mixture of toluene and THF (100 mL) kept at −78 °C. Additional DIBAL-H (5.0 mL, 6.1 mmol) was added after 1.5 h, and the stirring was continued for 1 h. Crushed ice (∼80 g) was added, and a heavy gelatinous substance formed when the mixture had reached ambient temperature. EtOAc (∼400 mL) was added, and the mixture was filtered when the precipitate had become flaky (∼5 h). The filtrate was dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography using EtOAc/*n*-hexane (3:2) as eluent. This gave 7.0 g (78%) of **6** as a 1:1 mixture of diastereomers: TLC R_f = 0.28 [EtOAc/*n*-hexane (3:2)]; ^{1}H NMR ($CDCl_3$) δ 0.05 and 0.06 (6H, s's, $Si(CH_3)_2$), 0.89 [9H, two peaks, $C(CH_3)_3$], 1.80−1.90, 2.00−2.06, 2.10−2.21, 2.25−2.34, 2.38−2.46 (1H, 1H, 1.5H, 1.5H, and 1H, respectively), 2.71 and 3.21 (0.5H each, app d and br s, respectively, OH), 3.52, 3.64, 3.71 (1H, 0.5H, 0.5H, respectively, m, dd, dd, respectively, CH_2OSi), 4.01−4.07 and 4.07−4.12 (0.5H each, each m, H_7), 4.62 and 4.66 (0.5H each, each m, H_1), 5.54 and 5.67 (0.5H each, each app d, H_3). Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.3; H, 9.95.

13-[(*tert*-Butyldimethylsilyl)oxy]-14,15,16, 17,18,19,20-heptanorprostaglandin $F_{2\alpha}$ (7). Potassium *tert*-butoxide (50.9 g, 453 mmol) was added to a stirred suspension of (4-carboxybutyl)triphenylphosphonium bromide (105.4 g, 238 mmol) in THF (250 mL) at −10 °C (dry ice bath). A solution of lactol **6** (28.6 g, 95 mmol) in THF (110 mL) was added to the deep orange colored ylide at −30 °C. The cooling bath was removed after 45 min, and water (∼250 mL) was added to the reaction mixture. Most of the formed Ph_3PO was removed (TLC; EtOAc) by extractions with ether (6 × 300 mL). The aqueous layer was made slightly acidic (pH ∼4.5) by addition of NaH_2PO_4 monohydrate and was extracted with EtOAc (4 × 500 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was filtered through a silica gel column by elution with ether. The main part (34.6 g) of the partially purified acid **7** was used directly in the next step. However, a small fraction (0.35 g) was purified on a second column using the same eluent. Analytical HPLC

(16) Andersen, N. H.; Imamoto, S.; Picker, D. H. *Prostaglandins* **1977**, *14*, 61−101.

(straight phase; mobile phase 8% ethanol in *n*-hexane, flow: 2 mL/min) and ^{13}C NMR spectroscopy showed that the product contained ~5% of the *trans* isomer. An analytical sample (49 mg) of isomerically pure **7** was obtained from 255 mg after 3 preparative HPLC (mobile phase 7.5% ethanol in *n*-hexane, flow: 11 mL/min) runs. TLC $R_f = 0.20$ (ether/methanol (95:5)]; $[\alpha]_D$ +41.1 (*c* 1.11, CH_3CN); ^1H NMR ($CDCl_3$) δ 0.04 and 0.05 [6H, s's, $Si(CH_3)_2$], 0.88 [9H, s, $C(CH_3)_3$], 1.60−1.75 (3H, m, $H_{3's}$ and H_8), 1.82−1.95 (3H, m, $H_{10's}$ and H_{12}), 2.07−2.24 (3H, m, $H_{4'}$ and $H_{7's}$), 2.31−2.38 (3H, m, $H_{2's}$ and $H_{4''}$), 3.50 (1H, dd, $H_{13'}$, $J = 5.8, 10.1$), 3.78 (1H, dd, $H_{13''}$, $J = 4.0, 9.9$), 4.05−4.32 (2H, br m, H_9 and H_{11}), 5.35−5.42 (1H, m, H_6), 5.42−5.49 (1H, m, H_5). Anal. Calcd for $C_{19}H_{36}O_5Si$: C, 61.25; H, 9.74. Found: C, 61.5; H, 9.65.

13-[(*tert*-Butyldimethylsilyl)oxy]-14,15,16,17,18,19,20-heptanorprostaglandin $F_{2\alpha}$ Isopropyl Ester (8). 2-Iodopropane (27.58 g, 162.3 mmol) was added to a stirred mixture of K_2CO_3 (11.03 g, 79.8 mmol) and partially purified acid **7** (10.7 g, ~26.6 mmol) in CH_3CN (60 mL) kept at 85 °C. More 2-iodopropane (3.0 g, 17.6 mmol) was added after 4 h, and the stirring was continued for 5 h. The reaction mixture was cooled to room temperature and ether (~200 mL) was added. Solids were removed by filtration, and concentration of the filtrate gave the crude ester **8** as an oil. Repetitive column chromatography using *n*-hexane/EtOAc (2:1) as eluent gave 7.26 g (66% from lactol **6**) of the title product. Analytical HPLC was performed on **8** (straight phase; mobile phase 2.2% ethanol in *n*-hexane, flow: 2 mL/min), and ^{13}C NMR spectroscopy indicated the presence of ~5% of the *trans* isomer. An analytical sample of isomerically pure **8** (140 mg) was obtained 190 mg after 4 preparative HPLC (mobile phase 3% ethanol in *n*-hexane, flow: 12 mL/min) runs. TLC $R_f = 0.30$ [*n*-hexane/EtOAc (3:2)]; $[\alpha]_D$ +38.2 (*c* 1.07, CH_3CN); ^1H NMR ($CDCl_3$) δ 0.04 and 0.05 [6H, s's, $Si(CH_3)_2$], 0.88 [9H, s, $C(CH_3)_3$], 1.23 (6H, d, $CH(CH_3)_2$, $J = 6.1$), 1.59−1.64 (1H, m, H_8), 1.69 (2H, quint, $H_{3's}$), 1.80−1.93 (3H, m, $H_{10's}$ and H_{12}), 2.07−2.16 (1H, m, $H_{7's}$), 2.16−2.24 (1H, m, $H_{4'}$), 2.28 (2H, t, $H_{2's}$, $J = 7.4$), 2.32−2.38 (1H, m, $H_{4''}$), 2.61 (1H, br, OH), 2.92 (1H, br, OH), 3.50 (1H, dd, $H_{13'}$, $J = 6.1, 10.0$), 3.78 (1H, dd, $H_{13''}$, $J = 4.6, 9.9$), 4.12 and 4.19 (each 1H, each m, H_9 and H_{11}), 5.00 (1H, sept, $CH(CH_3)_2$, $J = 6.1$), 5.36−5.42 (1H, m, H_6), 5.43−5.49 (1H, m, H_5). Anal. Calcd for $C_{22}H_{42}O_5Si$: C, 63.72; H, 10.21. Found: C, 63.65; H, 10.25.

14,15,16,17,18,19,20-Heptanorprostaglandin $F_{2\alpha}$ Isopropyl Ester (9). To a solution of partially purified ester **8** (7.18 g, 17.3 mmol) in THF (100 mL) was added $NaHSO_4 \cdot H_2O$ (9.56 g, 69.2 mmol) in water (50 mL). The mixture was stirred at room temperature for 13 h. Water (80 mL) and CH_2Cl_2 (300 mL) were added, and the resulting mixture was extracted. The aqueous layer was extracted with more CH_2Cl_2 (2 × 150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (80 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography afforded 4.98 g (96%) of **9** as an oil. Analytical HPLC (straight phase; mobile phase 6% ethanol in *n*-hexane, flow: 2 mL/min) and ^{13}C NMR spectroscopy indicated the precence of ~5% of the *trans* isomer. An analytical sample of isomerically pure **9** was obtained from 150 mg after 3 preparative HPLC (mobile phase 5.8% ethanol in *n*-hexane, flow: 15 mL/min) runs: TLC $R_f = 0.32$ [ether/methanol (95:5)]; $[\alpha]_D$ +43.0 (*c* 1.03, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.23 (6H, d, $CH(CH_3)_2$, $J = 6.3$), 1.45−1.51 (1H, m, H_8), 1.68 (2H, quint, $H_{3's}$), 1.85 (1H, m, $H_{10\beta}$), 1.90−1.98 (2H, m, $H_{10\alpha}$ and H_{12}), 2.12 (2H, app q, $H_{7's}$), 2.20−2.26 (1H, m, $H_{4'}$), 2.28 (2H, t, $H_{2's}$, $J = 7.3$), 2.31−2.38 (1H, m, $H_{4''}$), 2.89 (1H, d, OH, $J = 5.9$), 3.01 (1H, br s, OH), 3.45 (1H, app t, $H_{13'}$), 3.55 (1H, m, OH), 3.78 (1H, dd, $H_{13''}$, $J = 4.1, 10.6$), 4.17 (2H, m, H_9 and H_{11}), 5.00 (1H, sept, $CH(CH_3)_2$, $J = 6.3$), 5.37−5.42 (1H, m, H_6), 5.42−5.49 (1H, m, H_5). Anal. Calcd for $C_{16}H_{28}O_5$: C, 63.98; H, 9.39. Found: C, 63.6; H, 9.35.

15-Keto-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester (11). Phenylboronic acid (1.14 g, 9.39 mmol) was added to a mixture of **9** (1.27 g, 4.23 mmol), CH_2Cl_2 (30 mL) and molecular sieves (3 Å). The solution was stirred for 20 min at room temperature. Pyridinium chlorochromate (PCC; 3.0 g, 14.0 mmol) and Al_2O_3 (9.0 g) was mixed in a 250 mL roundbottom flask. Acetone (~100 mL) was added, and the solvent was evaporated in vacuo at 38 °C. The protected triol was added to the PCC−Al_2O_3 mixture, and more CH_2Cl_2 (50 mL) and molecular sieves were added. The reaction mixture was stirred for 3 h under N_2 and was then filtered through a short pad of SiO_2 (prewashed with ether). The product was eluted with ether, and the crude aldehyde **10** was obtained as a brown oil after concentration of the eluents.

A solution of diisopropylethylamine (DIPEA; 1.13 g, 8.71 mmol) in CH_3CN (10 mL) was added to a cold (−15 °C) stirred suspension of LiCl (0.91 g, 21.6 mmol) and dimethyl (2-oxo-4-phenylbutyl)phosphonate[2] (1.17 g, 4.57 mmol) and molecular sieves in CH_3CN (20 mL) under N_2. The mixture was stirred for 45 min, and a solution of the crude aldehyde **10** in CH_3CN (30 mL) was added. The reaction mixture was stirred for 30 min at −15 °C and then at room temperature overnight. Ether and $MgSO_4$ was added, and the mixture was filtered and concentrated. The residue was dissolved in THF (30 mL) and 30% aqueous H_2O_2 (8 mL) was carefully added. The reaction mixture was stirred for 15 min and was then extracted with EtOAc. The organic layer should be washed with a saturated aqueous solution of Na_2SO_3. The organic layer was washed with aqueous $NaHCO_3$ (2 × 30 mL), dried ($MgSO_4$), and concentrated by careful evaporation in vacuo at room temperature. Column chromatography (gradient system: CH_2Cl_2 to EtOAc) afforded 1.36 g (76%) of **11** as an oil: TLC $R_f = 0.33$ (EtOAc); $[\alpha]_D$ +46.7 (*c* 0.83, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, $CH(CH_3)_2$, $J = 6.3$), 1.62 (1H, m, H_8), 1.67 (2H, app quint, H_3), 1.86 (1H, m, $H_{10\beta}$), 2.0−2.30 (7H, m, H_4, H_7, $H_{10\alpha}$ and H_2), 2.53 (1H, m, H_{12}), 2.86−2.96 (4H, m, H_{16} and H_{17}), 4.04 (1H, br m, H_{11}), 4.22 (1H, app br t, H_9), 5.00 (1H, sept, $CH(CH_3)_2$, $J = 6.3$), 5.34−5.40 (2H, m, H_5 and H_6), 6.18 (1H, d, H_{14}, $J = 15.7$), 6.67 (1H, dd, H_{13}, $J = 9.2, 15.7$), 7.18−7.31 (5H, m, aromatic protons). Anal. Calcd for $C_{26}H_{36}O_5 \cdot 1/4H_2O$: C, 72.11; H, 8.38. Found: C, 72.2; H, 8.2.

15α-Hydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*S*)-1] and 15*β*-Hydroxy-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ Isopropyl Ester [(15*R*)-1]. A solution of **11** (1.36 g, 3.17 mmol) and cerium chloride heptahydrate (0.35 g, 0.95 mmol) in MeOH/CH_2Cl_2 (2:1, 50 mL) was stirred at −78 °C for 30 min under N_2. $NaBH_4$ (72.0 mg, 1.90 mmol) was added in small portions to the stirred reaction mixture during a period of 1 h. After being stirred at −78 °C for 1 h, the reaction mixture was acidified with 1 M aqueous HCl to pH 4 and concentrated. The crude product was extracted with EtOAc (50 mL), washed with brine (2 × 20 mL) and 3% aqueous citric acid (2 × 20 mL), dried ($MgSO_4$), and concentrated. The residue consisted of a diastereomeric mixture of (15*S*)-**1** and (15*R*)-**1** (α and *β* isomers). The epimers were separated by column chromatography (gradient system; CH_2Cl_2/EtOAc 3:1 to EtOAc) which furnished 0.63 g (46%) of isomerically pure (15*R*)-**1** and 0.52 g (38%) of isomerically pure (15*S*)-**1**.

(15*R*)-1: HPLC (8.5% ethanol in isohexane), 1.0 mL/min, $t_R = 16.0$ min; TLC $R_f = 0.23$ (EtOAc); $[\alpha]_D$ +21.1 (*c* 0.98, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, $CH(CH_3)_2$), 1.51 (1H, m, H_8), 1.66 (2H, app quint, H_3), 1.75−1,90 (3H, m, $H_{10\beta}$ and H_{16}), 2.10−2.35 (6H, m, $H_{10\alpha}$, H_4, H_7 and H_{12}), 2.26 (2H, app t, H_2), 2.72 (2H, m, H_{17}), 3.95 (1H, br m, H_{11}), 4.11 (1H, br m, H_{15}), 4.18 (1H, br m, H_9), 4.99 (1H, sept, $CH(CH_3)_2$), 5.36 (1H, m, H_5), 5.44 (1H, m, H_6), 5.51 (1H, m, H_{13}), 5.63 (1H, m, H_{14}), 7.15−7.31 (5H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_5 \cdot {}^1/_4H_2O$: C, 71.77; H, 8.80. Found: C, 71.7; H, 8.4.

(15*S*)-1: HPLC (8.5% ethanol in isohexane), 1.0 mL/min, $t_R = 17.9$ min; TLC $R_f = 0.13$ (EtOAc); $[\alpha]_D$ +27.4 (*c* 1.2, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.20 (6H, d, $CH(CH_3)_2$), 1.46 (1H, m, H_8), 1.64 (2H, app quint, H_3), 1.70 (1H, m, $H_{10\beta}$), 1.79 (1H, m, $H_{16'}$), 1.91 (1H, m, $H_{16''}$), 2.08 (3H, m, H_4 and $H_{7'}$), 2.23 (2H, app t, H_2), 2.24 (2H, m, $H_{7''}$ and $H_{10\alpha}$), 2.33 (1H, m, H_{12}), 2.67 (2H, m, H_{17}), 3.88 (1H, m, H_{11}), 4.07 (1H, m, H_{15}), 4.13 (1H, m, H_9), 4.97 (1H, sept, $CH(CH_3)_2$), 5.35 (1H, m, H_5), 5.43 (1H, m, H_6), 5.45 (1H, m, H_{13}), 5.59 (1H, m, H_{14}), 7.10−7.25 (5H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.89. Found: C, 72.5; H, 8.8.

Epoxidation of (15*S*)-1 Using (+)-L-Diisopropyl Tartrate. Preparation of 13*β*,14*β*-Epoxy-15α-hydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*S*)-2]. Titanium tetraisopropoxide (117 mg, 0.41 mmol)

and (+)-L-diisopropyl tartrate (116 mg, 0.49 mmol) were dissolved in CH_2Cl_2 (3 mL, dried over $MgSO_4$). The solution was stirred with molecular sieves (3 Å) at 0 °C for 20 min under N_2. Phenylboronic acid (136 mg, 1.12 mmol) was added to a stirred solution of (15*S*)-**1** (219 mg, 0.51 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 10 min and was then added to the above cold solution under N_2. After 20 min, *tert*-butyl hydroperoxide (0.63 mL, 2.54 mmol, 4 M in toluene) was added and the mixture was stirred for 10 min at 0 °C and then at room temperature for 2 h. The mixture was diluted with THF (5 mL) and treated with 30% aqueous H_2O_2 (0.5 mL). After 10 min, cold 10% aqueous citric acid (5 mL) was added and stirring was continued until the aqueous layer became clear (~20 min). The organic layer should be washed with a saturated aqueous solution of Na_2SO_3. The organic layer was washed with brine and aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated by careful evaporation in vacuo at room temperature. Column chromatography (EtOAc) gave 150 mg (66%) of an oily product which is a diastereomeric mixture of (15*S*)-**2** and (15*S*)-**3**. Analytical HPLC showed a 93% de of (15*S*)-**2**. Separation by preparative HPLC (5% ethanol in isohexane) gave 114 mg (50%) of isomerically pure (15*S*)-**2** as an oil: HPLC (9% ethanol in isohexane), 1.8 mL/min, t_R = 9.7 min; TLC R_f = 0.22 (EtOAc); $[\alpha]_D$ +1.4 (*c* 1.2, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, CH(CH_3)$_2$, J = 6.4), 1.63 (1H, m, H_8), 1.67 (2H, m, H_3), 1.80 and 1.91 (2H, m, H_{16}), 1.84 and 1.95 (2H, m, H_{10}), 1.84 (1H, m, H_{12}), 2.12 (2H, m, H_4), 2.28 (2H, app t, H_2), 2.30 and 2.38 (2H, m, H_7), 2.74 and 2.86 (2H, m, H_{17}), 2.86 (1H, dd, H_{14}, J = 2.2, 3.9), 3.03 (1H, dd, H_{13}, J = 2.2, 6.4), 3.74 (1H, m, H_{15}), 4.08 (1H, br m, H_{11}), 4.21 (1H, br m, H_9), 4.99 (1H, sept, CH(CH$_3$)$_2$, J = 6.4), 5.41 (1H, m, H_5), 5.45 (1H, m, H_6), 7.20 (3H, m, aromatic protons), 7.28 (2H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.9; H, 8.6. Found: C, 69.6; H, 8.4.

Epoxidation of (15*S*)-1 Using (−)-D-Diisopropyl Tartrate. Preparation of (15*S*)-2 and 13α,14α-Epoxy-15α-hydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*S*)-3]. Compounds (15*S*)-**2** and (15*S*)-**3** were prepared from (15*S*)-**1** (214 mg, 0.50 mmol) using (−)-D-diisopropyl tartrate by the above method. The reaction mixture was stirred at 0 °C for 12 h and then at room temperature for 4 h. The workup was done as above, and the product was purified by column chromatography (EtOAc) which furnished 136 mg (61%) of the product as a diastereomeric mixture of (15*S*)-**3** and (15*S*)-**2**. Analytical HPLC showed a 62% de of (15*S*)-**3**. Separation by preparative HPLC (6% ethanol in isohexane) gave 98 mg (44%) of isomerically pure (15*S*)-**3** as an oil and 19 mg (8%) of isomerically pure (15*S*)-**2** as an oil.

(15*S*)-3: HPLC (9% ethanol in isohexane), 1.8 mL/min, t_R = 12.2 min; TLC R_f = 0.22 (EtOAc); $[\alpha]_D$ +42.0 (*c* 1.0, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, CH(CH_3)$_2$, J = 6.1), 1.64 (1H, m, H_8), 1.66 (2H, m, H_3), 1.79 (1H, m, H_{12}), 1.84 and 1.90 (2H, m, H_{16}), 1.84 and 1.96 (2H, m, H_{10}), 2.09 (2H, m, H_4), 2.20 (1H, m, $H_{7'}$), 2.24 (2H, app t, H_2), 2.36 (1H, m, $H_{7''}$), 2.72 and 2.81 (2H, m, H_{17}), 2.86 (1H, dd, H_{13}, J = 2.2, 6.7), 2.93 (1H, dd, H_{14}, J = 2.2, 4.6), 3.54 (1H, m, H_{15}), 4.15 (1H, br m, H_{11}), 4.19 (1H, br m, H_9), 4.99 (1H, sept, CH(CH$_3$)$_2$, J = 6.1), 5.39 (1H, m, H_5), 5.43 (1H, m, H_6), 7.20 (3H, m, aromatic protons), 7.28 (2H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.9; H, 8.6. Found: C, 69.6; H, 8.4.

Epoxidation of (15*R*)-1 Using (−)-D-Diisopropyl Tartrate. Preparation of 13α,14α-Epoxy-15β-hydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*R*)-3]. Compound (15*R*)-**3** was prepared from (15*R*)-**1** (163 mg, 0.38 mmol) using (−)-D-diisopropyl tartrate by the above method. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. The workup was done as above and the product was purified by column chromatography (EtOAc) which furnished 130 mg (76%) of the product as a diastereomeric mixture of (15*R*)-**2** and (15*R*)-**3**. Analytical HPLC showed a 92% de of (15*R*)-**3**. Separation by preparative HPLC (5% ethanol in isohexane) gave 90 mg (53%) of isomerically pure (15*R*)-**3**: HPLC (9% ethanol in isohexane), 1.8 mL/min, t_R = 10.4 min; TLC R_f = 0.22 (EtOAc); $[\alpha]_D$ +55.8 (*c* 0.98, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, CH(CH_3)$_2$, J = 6.4), 1.65 (3H, m, H_8 and H_3), 1.77 (1H, m, H_{12}), 1.80 and 1.91 (2H, m, H_{16}), 1.85 and 1.96 (2H, m, H_{10}), 2.10 (2H, m, H_4), 2.25 (2H, app t, H_2), 2.25 and 2.35 (2H, m, H_7), 2.73 and 2.87 (2H, m, H_{17}), 2.91 (2H, m, H_{14} and H_{13}), 3.74 (1H, m, H_{15}), 4.18 (1H, m, H_{11}), 4.19 (1H, m, H_9), 4.99 (1H, sept, CH(CH$_3$)$_2$, J = 6.4), 5.40 (1H, m, H_5), 5.45 (1H, m, H_6), 7.20 (3H, m, aromatic protons), 7.28 (2H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.9; H, 8.6. Found: C, 69.7; H, 8.7.

Epoxidation of (15*R*)-1 Using (+)-L-Diisopropyl Tartrate. Preparation of 13β,14β-Epoxy-15β-hydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*R*)-2] and (15*R*)-3. Compound (15*R*)-**2** and (15*R*)-**3** were prepared from (15*R*)-**1** (241 mg, 0.56 mmol) using (+)-L-diisopropyl tartrate by the above method. The reaction mixture was stirred at 0 °C for 12 h and then at room temperature for 4 h. The workup was done as above and the product was purified by column chromatography (EtOAc) which furnished 153 mg (61%) of the product as a diastereomeric mixture of (15*R*)-**2** and (15*R*)-**3**. Analytical HPLC showed a 22% de of (15*R*)-**2**. Separation by preparative HPLC (4% ethanol in isohexane) gave 47 mg (19%) of isomerically pure (15*R*)-**3** as an oil and 52 mg (21%) of isomerically pure (15*R*)-**2** as an oil.

(15*R*)-2: HPLC (9% ethanol in isohexane), 1.8 mL/min, t_R = 10.7 min; TLC R_f = 0.22 (EtOAc); $[\alpha]_D$ +15.6 (*c* 1.1, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, CH(CH_3)$_2$, J = 6.5), 1.61 (1H, m, H_8), 1.68 (2H, m, H_3), 1.86 and 1.92 (2H, m, H_{16}), 1.88 (3H, m, H_{12} and H_{10}), 2.12 (2H, m, H_4), 2.27 (3H, m, $H_{7'}$ and H_2), 2.38 (1H, m, $H_{7''}$), 2.72 and 2.82 (2H, m, H_{17}), 2.86 (1H, dd, H_{14}, J = 2.2, 4.7), 2.96 (1H, dd, H_{13}, J = 2.2, 6.4), 3.52 (1H, m, H_{15}), 4.08 (1H, br m, H_{11}), 4.22 (1H, br m, H_9), 5.00 (1H, sept, CH(CH$_3$)$_2$, J = 6.5), 5.40 (1H, m, H_5), 5.45 (1H, m, H_6), 7.20 (3H, m, aromatic protons), 7.28 (2H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.9; H, 8.6. Found: C, 69.8; H, 8.5.

13α,14β,15α-Trihydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*S*)-12]. Phenylboronic acid (17.2 mg, 0.14 mmol) was added to a solution of (15*S*)-**2** (28.6 mg, 0.064 mmol) in THF (0.3 mL) and molecular sieves (3 Å) in a thin-necked Pyrex tube, sealed with a screw cap fitted with a Teflon gasket. After 10 min, LiOH (3.1 mg, 0.13 mmol) was added, and the mixture was flushed with N_2, sealed, and stirred at 80 °C for 24 h. The reaction mixture was diluted with THF (~0.5 mL) and was then treated with 30% aqueous H_2O_2 (0.3 mL). After being stirred for 10 min, the mixture was extracted with EtOAc (2 mL). The organic layer should be washed with a saturated solution of Na_2SO_3. The organic layer was washed with brine (2 mL), dried ($MgSO_4$), and concentrated by careful evaporation in vacuo at room temperature. Column chromatography (gradient system: EtOAc to EtOAc/acetone 2:1) afforded 17.8 mg (59%) of isomerically pure (15*S*)-**12** as an oil: HPLC (9% ethanol in isohexane), 1.8 mL/min, t_R = 18.3 min; TLC R_f = 0.12 (EtOAc); $[\alpha]_D$ +16.2 (*c* 0.80, CH_3CN); ^1H NMR (CD_3OD) δ 1.20 (6H, dd, CH(CH_3)$_2$, J = 1.5, 6.4), 1.65 (2H, app quint, H_3), 1.76 (1H, m, $H_{10\beta}$), 1.82 (1H, m, $H_{16'}$), 1.92 (2H, m, $H_{16''}$ and H_8), 1.97 (1H, m, $H_{10\alpha}$), 2.13 (3H, m, H_4 and H_{12}), 2.27 (2H, app t, H_2), 2.31 and 2.38 (2H, m, $H_{7'}$ and $H_{7''}$), 2.65 (1H, m, $H_{17'}$), 2.79 (1H, m, $H_{17''}$), 3.37 (1H, dd, H_{14}, J = 1.6, 8.6), 3.82 (1H, dd, H_{13}, J = 3.6, 8.6), 3.91 (1H, ddd, H_{15}, J = 1.6, 4.6, 8.8), 4.06 (1H, m, H_{11}), 4.13 (1H, app quart, H_9), 4.94 (1H, sept, CH(CH$_3$)$_2$, J = 6.4), 5.35 (1H, m, H_5), 5.59 (1H, m, H_6), 7.13 (1H, m, aromatic proton), 7.23 (4H, m, aromatic protons). Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 67.17; H, 8.66.

13β,14α,15α-Trihydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*S*)-13]. Isomerically pure (15*S*)-**13** was prepared from (15*S*)-**3** by the above method in 56% yield as an oil: HPLC (9% ethanol in isohexane), 1.8 mL/min, t_R = 12.6 min; TLC R_f = 0.19 (EtOAc); $[\alpha]_D$ +18.9 (*c* 0.53, CH_3CN); ^1H NMR (CD_3OD) δ 1.21 (6H, d, CH(CH_3)$_2$, J = 6.1), 1.65 (2H, app quint, H_3), 1.67 (1H, m, $H_{10\beta}$), 1.74 (1H, m, $H_{16'}$), 1.76 (1H, m, H_8), 2.03 (1H, m, $H_{16''}$), 2.08 (1H, m, $H_{10\alpha}$), 2.12 (3H, m, H_4 and H_{12}), 2.16 (1H, m, $H_{7'}$), 2.26 (3H, m, H_2 and $H_{7''}$), 2.64 (1H, m, $H_{17'}$), 2.86 (1H, m, $H_{17''}$), 3.60 (1H, dd, H_{14}, J = 6.7, 7.0), 3.71 (1H, ddd, H_{15}, J = 2.4, 6.7, 9.4), 3.82 (1H, dd, H_{13}, J = 2.0, 7.0), 4.10 (1H, m, H_9), 4.30 (1H, ddd, H_{11}, J

= 3.7, 6.1, 8.0), 4.95 (1H, sept, C*H*$(CH_3)_2$), 5.36 (1H, m, H_5), 5.54 (1H, m, H_6), 7.13 (1H, m, aromatic proton), 7.23 (4H, m, aromatic protons). Anal. Calcd for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 66.95; H, 8.62.

13α,14*β*,15*β*-Trihydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*R*)-12]. Isomerically pure (15*R*)-**12** was prepared from (15*R*)-**2** by the above method in 52% yield as an oil: HPLC (9% ethanol in isohexane), 1.8 mL/min, t_R = 13.9 min; TLC R_f = 0.22 (EtOAc); $[\alpha]_D$ +32.7 (*c* 0.85, CH_3CN); ^1H NMR (CD_3OD) δ 1.20 (6H, dd, CH(C*H*$_3)_2$, *J* = 6.1, 6.1), 1.65 (2H, app quint, H_3), 1.75 (2H, m, $H_{10\beta}$ and $H_{16'}$), 1.98 (3H, m, $H_{10\alpha}$, $H_{16''}$ and H_8), 2.13 (3H, m, H_4 and H_{12}), 2.29 (2H, app t, H_2), 2.35 (2H, m, H_7), 2.65 (1H, m, $H_{17'}$), 2.89 (1H, m, $H_{17''}$), 3.45 (1H, dd, H_{14}, *J* = 5.5, 8.5), 3.74 (1H, dd, H_{13}, *J* = 3.3, 8.5), 3.77 (1H, ddd, H_{15}, *J* = 2.4, 5.5, 8.2), 4.06 (1H, ddd, H_{11}, *J* = 4.3, 6.1, 8.5), 4.13 (1H, m, H_9), 4.95 (1H, sept, C*H*$(CH_3)_2$), 5.36 (1H, m, H_5), 5.59 (1H, m, H_6), 7.13 (1H, m, aromatic proton), 7.23 (4H, m, aromatic protons). Anal. Calcd for $C_{26}H_{40}O_7 \cdot {}^1/_4H_2O$: C, 66.57; H, 8.70. Found: C, 66.57; H, 8.62.

13*β*,14α,15*β*-Trihydroxy-17-phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*R*)-13]. Isomerically pure (15*R*)-**13** was prepared from (15*R*)-**3** by the above method in 60% yield as an oil: HPLC (9% ethanol in isohexane), 1.8 mL/min, t_R = 11.2 min; TLC R_f = 0.17 (EtOAc); $[\alpha]_D$ +46.6 (*c* 0.90, CH_3CN); ^1H NMR (CD_3OD) δ 1.21 (6H, d, CH(C*H*$_3)_2$), 1.65 (2H, app quint, H_3), 1.70 (1H, m, $H_{10\beta}$), 1.79 (1H, m, H_8), 1.81 (1H, m, $H_{16'}$), 1.91 (1H, m, $H_{16''}$), 2.04 (1H, m, $H_{10\alpha}$), 2.12 (3H, m, H_4 and H_{12}), 2.17 (1H, m, $H_{7'}$), 2.27 (3H, m, H_2 and $H_{7''}$), 2.68 (1H, m, $H_{17'}$), 2.82 (1H, m, $H_{17''}$), 3.52 (1H, dd, H_{14}, *J* = 2.5, 7.9), 3.80 (1H, dd, H_{13}, *J* = 2.1, 7.9), 3.84 (1H, m, H_{15}), 4.10 (1H, m, H_9), 4.28 (1H, m, H_{11}), 4.96 (1H, sept, C*H*$(CH_3)_2$), 5.36 (1H, m, H_5), 5.53 (1H, m, H_6), 7.13 (1H, m, aromatic proton), 7.23 (4H, m, aromatic protons). Anal. Calcd for $C_{26}H_{40}O_7 \cdot {}^1/_4H_2O$: C, 66.57; H, 8.70. Found: C, 66.65; H, 8.59.

14*β*,15α-Dihydroxy-13α-(phenylthio)-17-phenyl-18,19,-20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*S*)-14]. A solution of thiophenol (38.8 μL, 0.38 mmol) and sodium methoxide (20.4 mg, 0.38 mmol) in ethanol (99.6%, 0.8 mL) was stirred at 45 °C for 30 min. A solution of phenylboronic acid (33.7 mg, 0.28 mmol) and (15*S*)-**2** (56.2 mg, 0.13 mmol) in THF (0.8 mL) was stirred for 10 min. The protected epoxide was added to the above thiophenolate solution, and the mixture was stirred at 45 °C overnight. The reaction mixture was allowed to reach room temperature and was then treated with 30% aqueous H_2O_2 (0.75 mL). After stirring for 10 min, a saturated aqueous solution of Na_2SO_3 (1 mL) was added, and the mixture was stirred vigorously until all H_2O_2 was reduced (~30 min). The product was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (gradient system: CH_2Cl_2/EtOAc 3:1 to EtOAc) afforded 36.3 mg (52%) of isomerically pure (15*S*)-**16** as an oil: HPLC (8.5% ethanol in isohexane), 1.0 mL/min, t_R = 10.2 min; TLC R_f = 0.31 (EtOAc); $[\alpha]_D$ +47.7 (*c* 1.01, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.21 (6H, d, CH(C*H*$_3)_2$, *J* = 6.3), 1.63 (2H, m, H_3), 1.68 (1H, m, $H_{16'}$), 1.77 (1H, m, $H_{10\beta}$), 1.83 (1H, m, $H_{16''}$), 2.0−2.1 (4H, m, $H_{7'}$, H_8, and H_4), 2.15 (1H, m, $H_{10\alpha}$), 2.22 (2H, app t, H_2), 2.28 (1H, m, $H_{7''}$), 2.50 (1H, m, $H_{17'}$), 2.55 (1H, m, H_{12}), 2.81 (1H, m, $H_{17''}$), 3.60 (1H, m, H_{13}), 3.87 (1H, m, H_{14}), 3.98 (1H, m, H_{15}), 4.16 (1H, m, H_9), 4.25 (1H, m, H_{11}), 4.98 (1H, sept, C*H*$(CH_3)_2$, *J* = 6.3), 5.35 (2H, m, H_5 and H_6), 7.1−7.55 (10H, m, aromatic protons). Anal. Calcd for $C_{32}H_{44}O_6S$: C, 69.04; H, 7.97. Found: C, 68.86; H, 7.98

13*β*,15*β*-Dihydroxy-14α-(phenylthio)-17-phenyl-18,19,-20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*R*)-15]. Compound (15*R*)-**15** was prepared from (15*R*)-**2** with the above method, but with a reaction time of 3 days, and in a total yield of 33%: HPLC (8.5% ethanol in isohexane), 1.2 mL/min, t_R = 10.2 min; TLC R_f = 0.54 (EtOAc); $[\alpha]_D$ +34.2 (*c* 0.87, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.22 (6H, d, CH(C*H*$_3)_2$, J = 6.3), 1.66 (2H, app quint, H_3), 1.73−1.85 (3H, m, H_8 and H_{10}), 1.94 (1H, m, $H_{16'}$), 2.08 (2H, app q, H_4), 2.2−2.3 (5H, m, $H_{7'}$, H_2, $H_{16''}$ and H_{12}), 2.33 (1H, m, $H_{7''}$), 2.72 (1H, m, $H_{17'}$), 2.89 (1H, m, $H_{17''}$), 3.38 (1H, dd, H_{14}, *J* = 4.9, 5.9), 3.76 (1H, dd, H_{13}, *J* = 4.9, 8.2), 3.87 (1H, br m, H_{11}), 4.05 (1H, m, H_{15}), 4.17 (1H, br m, H_9), 5.00 (1H, sept, C*H*$(CH_3)_2$, *J* = 6.3), 5.37 (1H, m, H_5), 5.45 (1H, m, H_6), 7.18−7.43 (10H, m, aromatic protons). Anal. Calcd for $C_{32}H_{44}O_6S \cdot {}^3/_4H_20$: C, 67.40; H, 8.21. Found: C, 67.32; H, 7.73.

13α,15α-Dihydroxy-14*β*-(phenylthio)-17-phenyl-18,19,-20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*S*)-16]. Isomerically pure (15*S*)-**16** was prepared from (15*S*)-**3** by the above method in 66% yield as an oil: HPLC (8.5% ethanol in isohexane), 1.0 mL/min, t_R = 10.8 min; TLC R_f = 0.45 (EtOAc); $[\alpha]_D$ +13.8 (*c* 0.89, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.20 (6H, dd, CH(C*H*$_3)_2$, *J* = 2.3, 6.2), 1.66 (2H, m, H_3), 1.75 (1H, m, H_8), 1.8−1.9 (2H, m, H_{10}), 1.95 (1H, m, $H_{16'}$), 2.05 (2H, m, H_4), 2.21 (3H, m, $H_{16''}$ and H_7), 2.27 (2H, app t, H_2), 2.39 (1H, m, H_{12}), 2.70 (1H, m, $H_{17'}$), 2.85 (1H, m, $H_{17''}$), 3.40 (1H, dd, H_{14}, *J* = 6.0, 8.9), 3.83 (1H, br m, H_{13}), 4.05 (1H, br m, H_{15}), 4.18 (1H, br m, H_9), 4.30 (1H, br m, H_{11}), 4.94 (1H, sept, C*H*$(CH_3)_2$, *J* = 6.2), 5.38 (1H, m, H_5), 5.53 (1H, m, H_6), 7.15−7.48 (10H, m, aromatic protons). Anal. Calcd for $C_{32}H_{44}O_6S$: C, 69.04; H, 7.97. Found: C, 68.82; H, 7.84.

14α,15*β*-Dihydroxy-13*β*-(phenylthio)-17-phenyl-18,19,-20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*R*)-17] and 13α,15*β*-Dihydroxy-14*β*-(phenylthio)-17-phenyl-18,-19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester [(15*R*)-16]. Compounds (15*R*)-**17** and (15*R*)-**16** were prepared from (15*R*)-**3** by the above method, but with a reaction time of 3 days. This gave a total yield of 35%. Analytical HPLC on the crude product showed that the diastereomeric relationship was 69:31 (15*R*)-**17**:(15*R*)-**16**. Separation by column chromatography (gradient system: CH_2Cl_2 to CH_2Cl_2:EtOAc 5:1) furnished 11% of isomerically pure (15*R*)-**16** as an oil and 14% of isomerically pure (15*R*)-**17** as an oil.

(15*R*)-17: HPLC (8.5% ethanol in isohexane), 1.0 mL/min, t_R = 12.1 min; TLC R_f = 0.47 (EtOAc); $[\alpha]_D$ +33.7 (*c* 0.89, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.23 (6H, d, CH(C*H*$_3)_2$, *J* = 6.3), 1.68 (4H, m, H_3 and H_{16}), 1.88 (2H, m, $H_{10\beta}$ and H_8), 2.13 (3H, m, $H_{10\alpha}$ and H_4), 2.30 (4H, m, H_2, $H_{7'}$ and $H_{17'}$), 2.52 (2H, m, $H_{7''}$ and H_{12}), 2.73 (1H, m, $H_{17''}$), 3.62 (1H, dd, H_{13}, *J* = 3.3, 7.3), 3.74 (1H, m, H_{14}), 3.97 (1H, br m, H_{15}), 4.24 (2H, br m, H_9 and H_{11}), 5.00 (1H, sept, C*H*$(CH_3)_2$, *J* = 6.3), 5.41 (1H, m, H_5), 5.49 (1H, m, H_6), 6.99−7.43 (10H, m, aromatic protons). Anal. Calcd for $C_{32}H_{44}O_6S$: C, 69.04; H, 7.97. Found: C, 68.97; H, 7.93.

(15*R*)-16: HPLC (8.5% ethanol in isohexane), 1.0 mL/min, t_R = 11.0 min; TLC R_f = 0.51 (EtOAc); $[\alpha]_D$ +44.6 (*c* 0.63, CH_3CN); ^1H NMR ($CDCl_3$) δ 1.20 (6H, d, CH(C*H*$_3)_2$, *J* = 6.2), 1.66 (2H, m, H_3), 1.76 (1H, m, H_8), 1.87 (2H, m, H_{10}), 2.05 (2H, m, H_{16}), 2.10 (3H, m, H_4 and $H_{7'}$), 2.27 (3H, m, H_2 and $H_{7''}$), 2.36 (1H, m, H_{12}), 2.64 (1H, m, $H_{17'}$), 2.82 (1H, m, $H_{17''}$), 3.45 (1H, dd, H_{14}, *J* = 2.0, 8.5), 3.86 (1H, m, H_{13}), 4.18 (1H, br m, H_{15}), 4.20 (1H, br m, H_9), 4.38 (1H, br m, H_{11}), 4.96 (1H, sept, C*H*$(CH_3)_2$, *J* = 6.2), 5.38 (1H, m, H_5), 5.49 (1H, m, H_6), 7.12−7.48 (10H, m, aromatic protons). Anal. Calcd for $C_{32}H_{44}O_6S$: C, 69.04; H, 7.97. Found: C, 68.80; H, 7.87.

Supporting Information Available: ^{13}C NMR spectroscopic data and peak assignment of all compounds (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

JO960098T