Triply Convergent Synthesis of 15-(Phenoxymethyl) and 4,5-Allenyl Prostaglandins. Preparation of an Individual Isomer of Enprostil[1]

Owen W. Gooding,* Colin C. Beard, Gary F. Cooper, and David Y. Jackson†

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

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A triply convergent synthesis of the PGE_2 derivatives **1**, **3**, **4**, and **5**, containing either the 15-(phenoxymethyl) or the 15-amyl ω side chain and the 5,6-didehydro or the 4,5-allenyl α side chain, is described. This two-pot method employs organocopper reagents of the type $Li_2R_\omega CuCNMe$ to selectively introduce the ω side chain to enantiopure enone **6** followed by *in situ* trapping of the so-formed enolates as silyl enol ethers **22a** and **22b**. The key step is the alkylation of regiochemically defined lithium enolates, generated from the corresponding silyl enol ethers **22a** and **22b**, with the unsaturated α side chain triflates **8b** and **9c**. The method was found to be general for propargylic and allenic α side chains but unsuccessful for the cis allylic and saturated α side chains found in PGE_2 and PGE_1, respectively.

Introduction

Prostaglandins (PGs) comprise a class of extremely potent natural hormones which exhibit a myriad of biological activities.[2] In particular, the naturally occurring PGs of the E, F, and I series have been shown to influence a number of gastrointestinal functions.[2b] This activity has lead to the clinical development of a number of synthetic PG analogs for use in the treatment of peptic ulcer disease.[2c,d] One such preparation is enprostil,[3] a synthetic PGE_2 analog used for the treatment of gastric and duodenal ulcers.[4] Enprostil is composed of two racemates which differ from PGE_2 by the presence of the extra C-4,5 double bond (allene) in the α side chain and the replacement of the 15-amyl group by a 15-phenoxymethyl group in the ω side chain (Figure 1). The intent of these structural modifications was to enhance the therapeutic value by slowing metabolic decomposition, decreasing unwanted side effects, and increasing chemical stability.[2d,e] The four individual isomers of enprostil have been shown to exhibit vastly different biological activities *in vitro*[4] making the efficient diastereoselective synthesis of these isomers for further clinical evaluation a challenging and necessary goal. The allene moiety present in these compounds adds an additional element of chirality not present in natural PGs.

Of the numerous published approaches to PGs[5,6] the simplest and most elegant is the triply convergent "three-component coupling" pathway[6] wherein the entire carbon framework is assembled stereoselectively by tandem alkylation[7] of an appropriate optically active enone (Scheme I, path A). Pioneering efforts revealed that *direct* alkylation of the enolate **2**, produced by organocopper-mediated conjugate addition, with alkyl halides was too slow to be of practical synthetic use.[8] The reaction apparently followed path B leading to polyalkylation and other side products. This prompted the development of *indirect*, functionally modified methods employing more reactive aldehydes and nitroolefins as alkylating agents.[6] Other indirect methods based on the use of functionally modified cyclopentenones have also appeared.[9,10]

The long sought after *direct* alkylation of protected 4-hydroxy-2-cyclopenten-1-one has recently been demonstrated in the laboratories of Noyori[11] and Syntex.[12] The first successful application by Noyori et al.[11a] em-

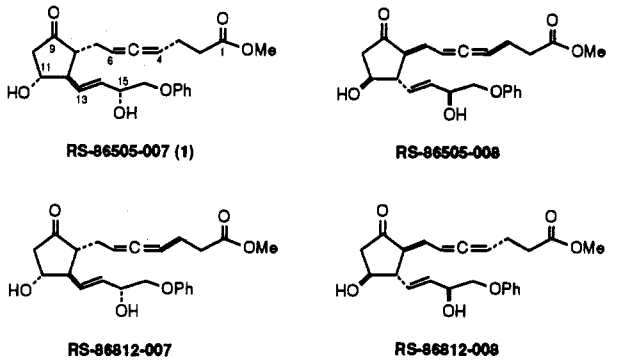

Figure 1. Four components of enprostil.

† Current Address: Genentech Inc., S. San Francisco, CA.

(1) Contribution No. 856 from the Institute of Organic Chemistry, Syntex Research. This manuscript is dedicated to Dr. John A. Edwards on the occasion of his retirement from Syntex Research.

(2) (a) Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* **1982**, Aug 16, 30. (b) Miller, T. A. *Am. J. Physiol.* **1983**, *245*, G601. (c) Bauer, R. F.; Collins, P. W.; Jones, P. H. *Ann. Rev. Med. Chem.* **1987**, *22*, 191. (d) Collins, P. W. *J. Med. Chem.* **1986**, 29, 437. (e) Muchowski, J. M. *CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids*; Willis, A. L., Ed.; CRC Press: Boca Raton, FL, 1987; Vol. 1, Part B, p 19.

(3) (a) Carpio, H.; Cooper, G. F.; Edwards, J. A.; Fried, J. H.; Garay, G. L.; Guzman, A.; Mendez, J. A.; Muchowski, J. M.; Roszkowski, A. P.; Van Horn, A. R.; Wren, D. *Prostaglandins* **1987**, *33*, 169. (b) Parnes, H. *J. Labelled Compd. Radiopharm.* **1990**, *28*, 29.

(4) (a) Eglen, R. M.; Whiting, R. L. *Br. J. Pharmacol.* **1989**, *98*, 1335 and references cited therein. (b) Grass, G. M.; Sweetana, S. A.; Bozarth, C. A. *J. Pharm. Pharmacol.* **1990**, *42*, 40 and references cited therein.

(5) For reviews see: (a) Caton, M. P. L. *Tetrahedron* **1979**, *35*, 2705. (b) Caton, M. P. L. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Roberts, S. M., Scheinmann, F., Eds.; Academic: New York, 1982. (c) Baxter, A. D.; Roberts, S. M. *Chem. Ind.* **1986**, 510.

(6) For an excellent review see: Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

(7) For a review see: Taylor, R. J. K. *Synthesis* **1985**, 364.

(8) (a) Patterson, J. W., Jr.; Fried, J. H. *J. Org. Chem.* **1974**, *39*, 2506. (b) Davis, R.; Untch, K. G. *Ibid.* **1979**, *44*, 3755.

(9) (a) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199. (b) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.

(10) (a) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655. (b) Johnson, C. R.; Penning, T. D. *Ibid.* **1988**, *110*, 4726.

(11) (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Ibid.* **1988**, *110*, 4718 and references cited therein. (c) Morita, Y., Suzuki, M., Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785.

(12) Gooding, O. W. *J. Org. Chem.* **1990**, *55*, 4209.

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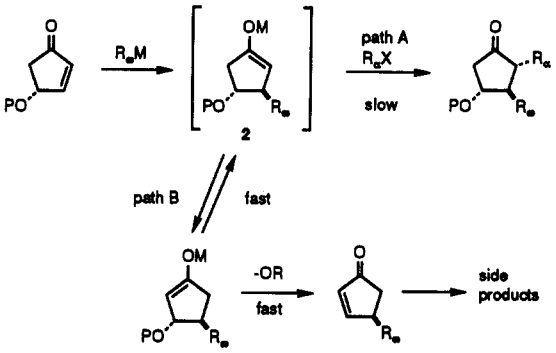
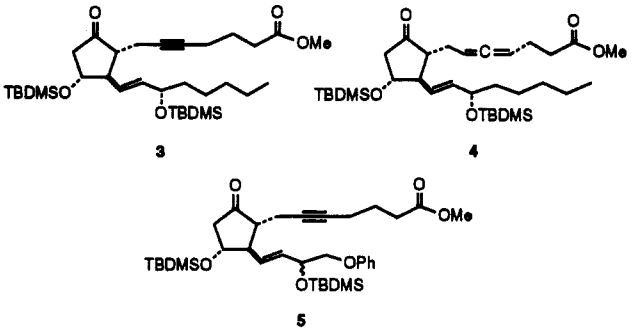
Scheme I



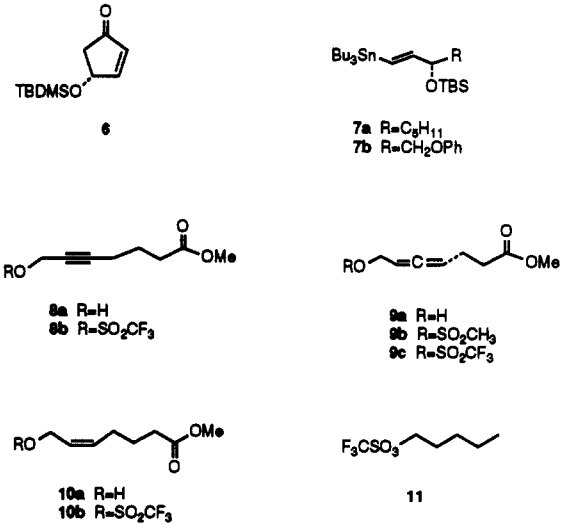
ployed copper to tin transmetalation at the enolate **2** stage affording a less basic stannyl enolate which retained its reactivity toward saturated, allylic, and propargylic α side chain iodides. Encouraged by this report, we attempted to apply the methodology to allenyl α side chain PGs only to find that the requisite α-iodoallene alkylating agents were inaccessible.[13] The use of a less reactive α-bromoallene gave the 4,5-didehydro PGE_2 derivative **4** in only 28% yield.[14] Less than 5% conversion was observed in systems containing the more sterically encumbered phenoxymethyl ω side chain present in enprostil.[15] This prompted us to look at leaving groups other than iodide to facilitate the alkylation of **2** with allenyl α side chains.

Recently, we reported a formal synthesis of several natural PGs employing a reactive α side chain propargylic triflate to alkylate a pure lithium enolate generated from the corresponding silyl enol ether.[12] The pivotal intermediate **3** was thus obtained in 65% isolated yield. We now describe the extension of this methodology to the synthesis of three other PGE_2 derivatives **1**, **4**, and **5** containing the 15-(phenoxymethyl) ω side chain and/or the 4,5-allenyl α side chain including RS-86505-007 (**1**), the most active isomer of enprostil.



Results and Discussion

Substrate Synthesis. The requisite enantiomerically pure enone, (*R*)-4-(*tert*-butyldimethylsiloxy)-2-cyclopentenone (**6**), was most efficiently prepared from the corresponding alcohol[16] using a recently described silyl-exchange method.[17] The ω side chain unit **7a** and the α side chain unit **8a** used in the synthesis of PGs in the natural series were prepared as previously described.[12]



The optically active allenic α side chain unit **9a** was prepared in >94% ee from D-mannitol as recently described by this laboratory.[18] The ω side chain **7b**, containing the 15-(phenoxymethyl) group, was synthesized as shown in Scheme II. Jones oxidation of the racemic propargylic alcohol **12**[19] afforded the prochiral ynone **13** as a crystalline solid (62%). Asymmetric reduction of the ynone[20] **13** using neat (*R*)-Alpine-Borane[21] gave the *R*-alcohol **14** in 83% yield.[22] Inversion of the hydroxyl function was most conveniently achieved using the Mitsunubo protocol[23] through the crystalline 3,5-dinitrobenzoate ester **15**. Enantiopure **15** was then isolated in 47% yield by repeated recrystallizations to a constant melting point. Basic hydrolysis of ester **15** afforded the desired *S*-alcohol **16** which was then protected as the TBDMS ether **17** in quantitative overall yield. Hydrostannylation of the alkyne **17** as previously described[19] afforded the desired *trans* olefin **7b** in 86% isolated yield.

Conjugate Addition/Enolate Trapping. In connection with triply convergent PG syntheses, a number of excellent ω side chain containing organometallic reagents have been developed.[10,11,24-27] In our hands, the most uniformly efficient reagents were the mixed, higher-order cuprates **19a** and **19b** prepared by ligand exchange between

(13) A thorough literature search revealed no reference to α-iodoallenes. Numerous attempts to prepare such compounds in our laboratories from the corresponding alcohols and bromides were unsuccessful.

(14) For an application of Noyori's method to the synthesis of a diastereomeric mixture of 4,5-didehydro-PGE_2: Patterson, J. W. *J. Org. Chem.* **1990**, *55*, 5528. For a different approach to 4,5-allenylprostaglandins see: Crabbé, P.; Carpio, H. *J. Chem. Soc., Chem. Commun.* **1972**, 904.

(15) Gooding, O. W., unpublished results.

(16) Both the *R* and *S* enantiomers of 4-hydroxy-2-cyclopentenone are available through either optical resolution or asymmetric reduction (see ref 11b). The material used in this study was obtained from Sumitomo Chemical Co.

(17) Takahashi, K.; Shiro, M.; Kishi, M. *J. Org. Chem.* **1988**, *53*, 3098.

(18) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083.

(19) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L. *Synthesis* **1986**, 496.

(20) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

(21) Registered trademark of Aldrich Chemical Co.

(22) At the time this work was performed the commercially available (*R*)- and (*S*)-Alpine-Boranes were of 91+% and 87% optical purity, respectively. Because the optical purity of the reduced substrates could, at best, have these optical purities, we chose to use the (*R*)- rather than the (*S*)-Alpine-Borane. We anticipated that the optical purity could be upgraded by recrystallization during the Mitsunobu inversion with little loss in overall yield.

(23) Mitsunobu, O. *Synthesis* **1981**, 1.

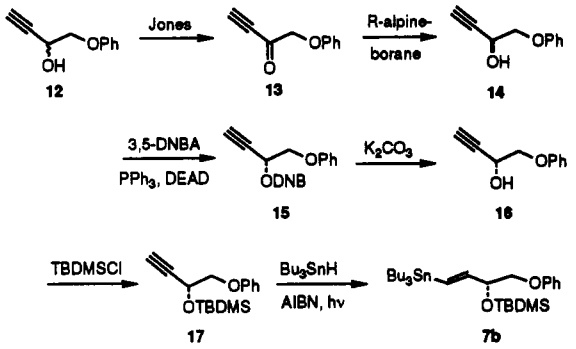
(24) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

(25) Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7441.

(26) Johnson, C. R.; Chen, Y. F. *J. Org. Chem.* **1991**, *56*, 3344.

(27) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Isr. J. Chem.* **1984**, *24*, 118.

Scheme II



$Li_2CuCNMe_2$ (18) and the appropriate vinyl stannane **7a** or **7b** (Scheme III).[24] Thus, treatment of 18 with stannane **7a** (0 °C, 1 h) gave a clear solution of cuprate **19a**. This exchange reaction was conveniently monitored by following the disappearance of **7a** by TLC analysis of quenched aliquots. Cooling of this solution (1.3 equiv) to −70 °C followed by treatment with enone **6** (1 equiv) for 5 min and a simple aqueous quench afforded the conjugate addition adduct **21a** in 92% isolated yield. This material was determined to be a single diastereoisomer using ^{13}C NMR spectroscopy.[28] Similarly, the reaction of phenoxy stannane **7b** afforded the conjugate addition adduct **21b** in 93% isolated yield. In contrast, the application of the phosphine-stabilized cuprate reagents[11,27] to these conversions gave **21a** and **21b** in 79% and 56% yields, respectively.

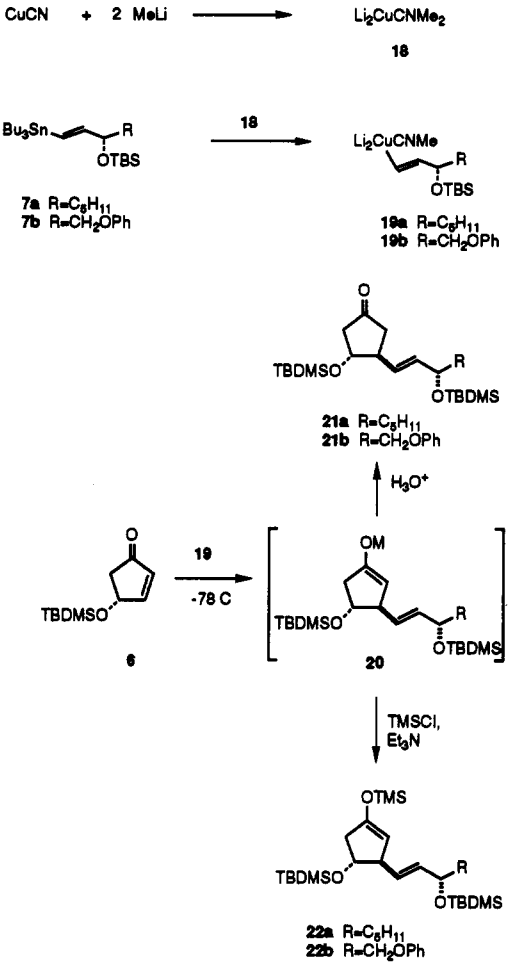
Trapping of the regiochemically defined enolates **20** as silyl enol ethers **22** was achieved by sequential treatment of the enolate with TMSCl (5 equiv) and triethylamine (10 equiv) followed by an aqueous workup to remove metal salts. Enol ethers **22a** and **22b** were relatively stable oils which slowly decomposed to the parent ketones on silica gel (TLC or column) making further purification impractical. The crude materials contained the byproducts methyltributyltin and traces of decomposition products derived from the excess cuprate, as judged by NMR spectroscopy. Fortunately, these impurities did not interfere with the subsequent alkylation reaction.

Enolate Regeneration. The silyl enol ethers **22a** and **22b** were readily converted into the corresponding lithium enolates by treatment with methyllithium in THF. The extent of enolate equilibration (Scheme I, path B) was minimized by brief exposure (10–13 min) to 1.4 equiv of MeLi at the relatively warm reaction temperature of −23 °C. After this period the lithium enolate solution was rapidly cooled to −70 °C and immediately treated with a solution of electrophile. In order to probe the efficiency of the silyl trapping/enolate regeneration sequence, an aqueous quench was used and the yield of recovered conjugate addition adduct determined by chromatographic isolation. The enol ether **22b** afforded the ketone **21b** in 82% yield (based on the enone employed in the conjugate addition reaction) following such treatment. Because the conjugate addition was shown to occur in 93% yield *vide supra*, the yield for the silyl trapping/enolate regeneration was 88% of theory. This result is noteworthy due to the propensity of β-substituted, 5-membered ring enolates to undergo equilibration/elimination even at −78 °C.[6,8]

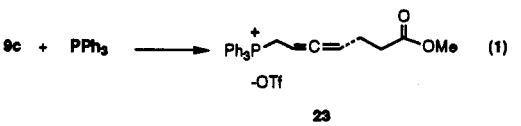
Triflate Formation. Sulfonic esters were selected as candidates because of their accessibility and excellent

(28) The spectrum was identical to that reported by Noyori (see ref 11b).

Scheme III



nucleofugacity in the alkylation reactions. The allenic mesylate **9b** was prepared in high yield from the corresponding alcohol **9a** by treatment with methanesulfonyl chloride and triethylamine; however, it failed to give efficient alkylation of the lithium enolate. The next logical step was the synthesis of the triflate **9c**, as triflates have been established to be some 2×10^4 times more reactive than mesylates in terms of leaving group ability.[29] Treatment of alcohol **9a** with triflic anhydride in the presence of pyridine[30] at low temperature led to the complete disappearance of starting alcohol **9a** by TLC. Several attempts to isolate products using aqueous and nonaqueous workup methods were unsuccessful. Assuming that the triflate may have formed and thermally decomposed upon attempted workup the reaction mixture was treated directly at low temperature with excess triphenylphosphine (eq 1).[30a] Thus, the triphenylphosphonium salt **23** was



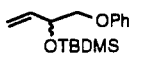
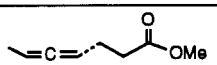
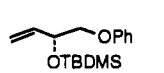
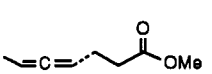
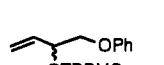
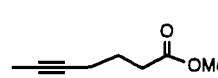
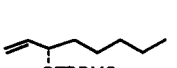
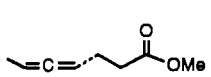
(1)

isolated in low yield. Further experimentation showed that nearly quantitative conversion could be achieved using

(29) Review: Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

(30) Modification of reported procedures: (a) Vedejs, E.; Engler, D. A.; Mullins, M. L. *J. Org. Chem.* **1977**, *42*, 3109. (b) Beard, C. D.; Baum, K.; Grakauskas, V. *J. Org. Chem.* **1973**, *38*, 3673.

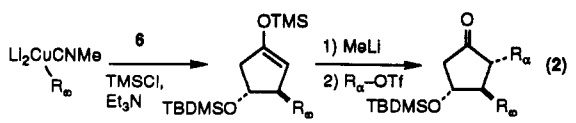
Table I. Tandem Alkylation of Enone 6 According to Eq 2

Rω	Rα	yield[a]
		68%[b]
		56 %
		56 %[b,c]
		47 %[c]
		65 %[d]

[a] Refers to isolated yield of analytically pure product. [b] Racemic enone was employed. [c] Results are from a single experiment. [d] Experimental details were provided in an earlier paper; see ref 12.

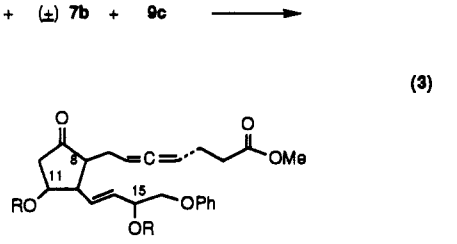
the hindered base 2,6-di-*tert*-butylpyridine (DTBP) at −42 °C. Similar conditions (DTBP, −23 °C) allowed the synthesis of the propargylic triflate **8b**[31] and the saturated triflate **11** in high yield. Due to their instability, these triflates were prepared and used immediately in the alkylation reactions described below. Numerous attempts to prepare the allylic triflate **10b** from the corresponding *cis* allylic alcohol **10a**[11a] were unsuccessful. A brief study was initiated using *cis*- and *trans*-hex-2-en-1-ol as models. Under the above conditions the *trans* compound was readily converted to the corresponding triflate while the *cis* compound did not react. Under more forcing conditions, the *cis* compound underwent decomposition. The reason for the vast difference in behavior has not been elucidated as further investigation was beyond the scope of this study.

Enolate Alkylation. The final step in this PG synthesis was the coupling of the lithium enolates containing either the 15-amyl or the 15-(phenoxymethyl) groups with the triflates containing either the α-allenic or the α-propargylic groups. The conversion of the silyl enol ethers **22a** and **22b** to the corresponding lithium enolates and the formation of the triflates **8b** and **9c** were best carried out concurrently so that the enolate solution could be treated immediately with the triflate solution. Results for the tandem alkylation sequence (eq 2) are given in Table I.



(2)

Optimization of the reaction conditions was conducted using racemic 15-(phenoxymethyl) ω side chain **19b**, racemic enone **6**, and optically pure allenyl triflate **9c**. The coupling of these components afforded the expected mixture of four diastereoisomers **24**, **25**, **26**, and **27** in up to 68% isolated yield based on enone **6** (eq 3). ^{13}C NMR



24: 8α, 11α, 12β, 15α
25: 8β, 11β, 12α, 15β
26: 8α, 11α, 12β, 15β
27: 8β, 11β, 12α, 15α

and HPLC analysis of this mixture showed the presence of a 3:3:2:2 mixture of silyl ethers with the RS-86505-007 (**24**) and RS-86812-008 (**25**) derivatives predominating.[32] This modest diastereoselectivity indicated that only minimal kinetic discrimination occurred in the conjugate addition reaction from the interaction between the 11- and the 15-(silyloxy) groups. The coupling of the corresponding enantiopure components gave the desired silyl ether **24** as a single diastereoisomer in 56% isolated yield. Desilylation of **24** using HF in the presence of pyridine gave RS-86505-007 (**1**), the most biologically active component of enprostil, in 67% yield. This material displayed physical properties identical to an authenic sample.[33] RS-86505-008, the enantiomer of **1**, would thus be obtained by coupling the enantiomeric components. The other two diastereomeric components of enprostil should also be available by selecting the appropriately configured components. The other three PGE_2 derivatives **3**, **4**, and **5** containing the various side chains were obtained in comparable yields. The less reactive saturated triflate **11** failed to give alkylation under these conditions.

In conclusion, we have developed the first triply convergent synthesis of an individual isomer of enprostil. This component bears an optically active allene moiety in the α side chain in addition to the other four stereocenters present in natural prostanoids. The method was found to have general applicability to the synthesis of PGE_2 derivatives containing either the 15-(phenoxymethyl) or the 15-amyl ω side chain and the 5,6-didehydro or the 4,5-allenyl α side chains. This technique was unsuccessful for the introduction of the α side chain containing the 4,5 cis double bond present in PGE_2 (due to the inability to prepare the requisite triflate) and the saturated chain present in PGE_1 (due to the low reactivity of saturated triflates). The experimental procedure also offers several practical advantages over previously developed technologies.[8-11] It is expeditious, requiring shorter reaction times and less expensive and/or hazardous reagents. Only minimal excesses of valuable ω and α side chain components are required, and the use of the mutagenic cosolvent HMPA is avoided entirely.

(31) Treatment of this reaction mixture with triphenylphosphine afforded an inseparable mixture of the expected propargylic phosphonium salt and the salt tentatively identified as the allene resulting from S_N2' attack on the triple bond.

(32) ^{13}C NMR spectroscopic analysis of this mixture clearly showed measurable chemical shift differences for C-12, C-13, and C-15 (PG numbering). By using the ratio of peak intensities for a given carbon resonance, the composition was determined to be roughly equal. This result was verified by desilylation and reapplication of the method to the corresponding mixture of diols. Finally, HPLC analysis of the mixture of diols more precisely showed the presence of a 3:3:2:2 mixture with the RS-86505-007 (**24**) and the RS-86812-008 (**25**) derivatives predominating.

(33) (a) Cooper, G. F.; Wren, D. L.; Van Horn, A. R.; Li, T. T.; Beard, C. C. Eur. Patent 146935, 1985; *Chem. Abstr.* **1986**, *104*(5), 33935c. (b) Cooper, G. F.; Wren, D. L.; Beard, C. C.; Galeazzi, E.; Van Horn, A. R.; Li, T. T. *J. Org. Chem.*, in press.

Experimental Section[34]

Elemental analyses were performed by the Analytical and Environmental Research group, Syntex Research. Radial chromatography was performed on a Harrison Research Chromatotron 7924 using silica gel plates (No. 7749, Kieselgel 60 PF_{254}, Merck). Silica gel thin-layer chromatography (TLC) plates were purchased from Analtech, and the Kieselgel 60 silica gel used for column chromatography was purchased from Merck. High-performance liquid chromatography (HPLC) was conducted using a Macherey-Nagel Nucleosil 100 silica column, 5 μm (250 × 4.6 mm); mobile phase, 2:25:400 MeOH/THF/CH_2Cl_2; flow rate, 2.0 mL/min; column temperature, 40 °C; detection, UV (270 nm). J values for ^1H NMR data are given in Hz. Trifluromethanesulfonic anhydride (Aldrich) was used from freshly opened ampules. Methyllithium (Aldrich) was used directly from the bottle after concentration was determined by titration. Optically pure (*S,E*)-3-[(*tert*-butyldimethylsilyl)oxy]-1-(tributylstannyl)-1-octene was prepared as previously described.[9a] (*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-cyclopentenone was prepared from the corresponding alcohol (Sumitomo) by a reported procedure.[17] Methyl 7-hydroxy-5-heptynoate[12] and (*R*)-methyl-7-hydroxy-4,5-heptadienoate[18] were prepared as previously described. All other reagents were used as received.

4-Phenoxy-1-butyn-3-one (13). A solution of 4-phenoxy-1-butyne-3-ol (20.0 g, 124 mmol) in acetone (150 mL) was cooled to 0 °C and treated with Jones reagent (125 mL, 250 mmol, 2.0 M) added at such a rate to keep the temperature below 5 °C. Stirring continued for 1 h at which time the excess oxidizing agent was destroyed by the addition of methanol (10 mL). An extractive aqueous workup (ethyl ether) gave 18.0 g of crude material which was purified by silica gel chromatography (5:95 → 10:90 ethyl acetate–hexanes) affording 12.1 g of **13** as a crystalline solid (62%): mp 47.5–48.5 °C; IR (KBr) 3210, 2074, 1700, 1251 cm^{-1}; ^1H NMR δ 3.39 (s, 1H), 4.72 (s, 2 H), 6.86–7.30 (m, 5 H); ^{13}C NMR δ 73.38, 79.01, 82.49, 114.72 (2 C), 121.97, 129.60 (2 C), 157.46, 182.59; MS m/z 160 (M^+), 131, 107, 77. Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.66; H, 5.14.

(*R*)-4-Phenoxy-1-butyn-3-ol (16). (*R*)-Alpine-Borane (375 mL, 188 mmol, 0.5 M in THF) was concentrated by rotary evaporation under vacuum with a nitrogen bleed until THF no longer distilled. The flask was filled with nitrogen and charged with ketone **13** (10.0 g, 62.5 mmol) and a magnetic stirring bar. This mixture was stirred 15 h at ambient temperature, diluted with ethyl ether (200 mL), and cooled to 0 °C. The excess reducing agent was destroyed by the addition of acetaldehyde (15 mL). An extractive aqueous workup (ethyl ether) followed by silica gel chromatography (10:90 ethyl acetate–hexanes) afforded 8.4 g of **14** (83%). A mixture of **14** (8.0 g, 49.4 mmol), triphenylphosphine (15.5 g, 60.0 mmol), and 3,5-dinitrobenzoic acid (12.6 g, 60.0 mmol) in toluene (350 mL) was cooled to 0 °C with stirring. This mixture was treated with diethyl azodicarboxylate (10.4 g, 60.0 mmol) added dropwise so as to maintain the internal temperature below 30 °C. Stirring continued at ambient temperature for 16 h at which time the mixture was transferred to a separatory funnel and washed successively with saturated aqueous $NaHCO_3$, water, and brine and dried over Na_2SO_4. Concentration *in vacuo* afforded 44 g of crude material which was purified by silica gel chromatography (dichloromethane) followed by repeated recrystallations (1:99 HOAc–methanol) to a constant sharp melting point of 160 °C. A total of 8.60 g of **15** was obtained as white needles (47%). This material (8.60 g, 23.0 mmol) was taken into THF (100 mL) and methanol (100 mL) containing 0.20 g of potassium carbonate, stirred at ambient temperature for 1 h, and then acidified with acetic acid (1 mL). Concentration followed by silica gel chromatography (3:97 ethyl acetate–hexanes) gave 4.20 g of **16** as a crystalline solid (100%): mp 48.5–50.0 °C; IR (KBr) 3414 (br), 3282, 2085, 1254 cm^{-1}; $[\alpha]^{25}_D$ −4.4 (*c* 2.7, MeOH); ^1H NMR δ 2.51 (d, J = 2.35 Hz, 1 H exchanges with D_2O), 2.94 (d, J = 5.50 Hz, 1 H), 4.08 (m, 2 H), 4.74 (m, 1 H), 6.90–7.29 (m, 5 H); ^{13}C NMR δ 61.04, 71.26, 74.32, 81.20, 114.72 (2 C), 121.45, 121.50 (2 C), 158.01; MS m/z 162 (M^+), 145, 107, 94, 77. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.07; H, 6.28.

(34) For general experimental procedures see ref 12.

(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-phenoxy-1-butyne (17). To a stirred solution of **16** (3.7 g, 23 mmol) and imidazole (3.1 g, 46 mmol) in DMF (50 mL) was added *tert*-butyldimethylsilyl chloride (5.2 g, 34 mmol) in one portion. This mixture was stirred for 1 h, diluted with water (100 mL), and extracted with ether (2 × 100 mL). The combined organic solutions were washed with water (2 × 75 mL) and dried ($MgSO_4$). Concentration followed by silica gel chromatography (2:98 ethyl acetate–hexanes) afforded 6.0 g of **17** as a clear oil (95%): IR (neat) 3325, 1588, 1249 cm^{-1}; $[\alpha]^{25}_D$ +40.0 (*c* 0.5, MeOH), ^1H NMR δ 0.13 (s, 3 H), 0.17 (s, 3 H), 0.92 (s, 9 H), 2.45 (d, J = 2.35, 1 H), 2.94 (d, J = 5.50, 1 H), 4.06 (ddd, J = 3.80, 7.05, 9.70, 2 H), 4.73 (m, 1 H), 6.94 (m, 3 H), 7.27 (m, 2 H); ^{13}C NMR δ −4.94, −4.80, 18.31, 25.72 (3 C), 62.19, 72.04, 73.39, 82.44, 114.7 (2 C), 121.06, 129.47 (2 C), 158.55; MS m/z 219 ($M^+ - C_4H_9$), 179, 151, 145, 94. Anal. Calcd for $C_{16}H_{24}O_2Si$: C, 69.52; H, 8.75. Found: C, 69.83; H, 8.70.

(*R,E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1-(tributylstannyl)-4-phenoxy-1-butene (7b). A mixture of **17** (6.00 g, 21.7 mmol), tributyltin hydride (11.4 g, 39.1 mmol), and 4,4′-azobis(4-cyanovaleric acid) was placed in a 130 °C oil bath with stirring. When the internal temperature reached 100 °C the exothermic reaction caused the internal temperature to rise rapidly to 160 °C. Stirring continued for 1 h at which time the excess tributyltin hydride was removed by vacuum distillation (bp 90 °C/1 Torr). The residue was allowed to cool to ambient temperature and purified by silica gel chromatography (100% hexanes) affording 10.6 g of **7b** as a clear liquid (86%): IR (neat) 1601, 1588, 1248, 669 cm^{-1}; $[\alpha]^{25}_D$ −13.1 (*c* 1.0, $CHCl_3$); ^1H NMR δ 0.09 (s, 6 H); 0.90 (m, 24 H); 1.30 (sext, J = 7.35, 6 H), 1.50 (m, 6 H), 3.85 (dd, J = 7.35, 9.50, 1 H), 3.88 (dd, J = 4.55, 9.65, 1 H), 4.49 (m, 1 H), 6.02 (dd, J = 5.00, 19.0, 1 H), 6.32 (dd, J = 1.40, 19.0, 1 H), 6.90 (m, 3 H), 7.26 (m, 2 H); ^{13}C NMR δ −4.62 (2 C), 9.52 (3 C), 13.7 (3 C), 18.5, 25.9 (3 C), 27.3 (3 C), 29.1 (3 C), 72.3, 74.7, 114.6 (2 C), 120.6, 129.4 (2 C), 129.6, 147.1, 159.0; MS m/z 567 (M^+), 511, 291, 193. Anal. Calcd for $C_{28}H_{52}O_2SiSn$: C, 59.26; H, 9.24. Found: C, 58.97; H, 9.12.

Triflate Preparation: General. A dry 25-mL flask equipped with an efficient magnetic stirring bar was cooled to the indicated temperature under nitrogen. Trifluoromethanesulfonic anhydride (0.502 g, 1.78 mmol) was added followed by the dropwise addition of a mixture of the appropriate alcohol (1.70 mmol) and 2,6-di-*tert*-butylpyridine (0.344 g, 1.80 mmol) in dichloromethane (1.5 mL) over 3 min. The sample vial was rinsed with dichloromethane (0.5 mL) and stirring continued for 5 min. The mixture was treated dropwise with hexanes (10 mL) and then placed in a −70 °C bath with vigorous stirring for 10 min. The thick suspension was filtered through a 2-mm pad of anhydrous sodium sulfate into a precooled (−70 °C) 25-mL pear-shaped flask, and the pad was rinsed with hexanes (3 mL). This flask was quickly vacuum purged with nitrogen affording a clear solution.

Triflate (9c) was prepared from 0.265 g of allenic alcohol **9a** at −42 °C. Attempts to isolate **9c** lead to decomposition.

Phosphonium Salt (23). The triflate solution was treated with triphenylphosphine (0.472 g, 1.80 mmol) in 5 mL of dichloromethane for 5 min at −70 °C. The cooling bath removed, and the mixture was allowed to warm to room temperature. Concentration gave an oil which was taken into ethyl acetate (40 mL) and washed with saturated aqueous sodium bicarbonate 2 × 25 mL, dried over ($MgSO_4$), and concentrated to 0.935 g of clear oil (100%). Attempts to crystallize this material were unsuccessful. An analytical sample was obtained by radial chromatography on silica using (30:70) acetone–dichloromethane as eluant: IR (neat) 1965, 1732, 1487, 1265, 1154, 1030 cm^{-1}; $[\alpha]^{25}_D$ −53.8 (*c* 2.2, MeOH); ^1H NMR δ 2.08 (m, 2 H), 2.23 (t, J = 7.0, 2 H), 3.65 (s, 3 H), 4.10 (m, 2 H), 5.13 (m, 2 H), 7.75 (m, 15 H); ^{13}C NMR 22.9, 23.8, 24.2, 32.6, 51.5, 79.8, 92.8, 117.2 (3 C), 130.4 (6 C), 133.3 (6 C), 135.2 (3 C), 172.8, 208.1; MS m/z 401 (M^+), 327, 275, 262, 183, 108. Anal. Calcd for $C_{27}H_{26}O_5F_3PS$: C, 58.91; H, 4.76. Found: C, 59.03, H, 4.90.

Triflate (8b) was prepared from 0.265 g of acetylenic alcohol **8a** at −23 °C. Attempts to isolate **8b** lead to decomposition.

Conjugate Addition/Enolate Trapping: General. To a dry 25-mL flask was added copper(I) cyanide (0.116 g, 1.30 mmol) and a magnetic stirring bar. The flask was capped with a rubber septum and heated with a heat gun under vacuum to remove any

traces of water, allowed to cool, and filled with nitrogen. Dry THF (3 mL) was added, and the suspension was cooled to 0 °C and vacuum purged with nitrogen several times. Methyllithium (2.0 mL, 2.8 mmol, 1.4 M in Et_2O) was added *via* syringe and stirring continued for 15 min during which time the suspension became clear and homogeneous. The appropriate stannane (1.40 mmol) dissolved in THF (1 mL) was added in one portion and stirring continued for the indicated time and temperature. The resulting cuprate solution was cooled to −70 °C and treated with a solution of enone **6** (0.212 g, 1.00 mmol) in THF (1 mL) added over 1 min. After 5 min chlorotrimethylsilane (0.543 g, 5.00 mmol) was added dropwise, stirring continued for 15 min, and triethylamine (1.01 g, 10.0 mmol) was added. The cooling bath was removed and the mixture allowed to warm to 0 °C when it was poured into a mixture of water (50 mL) and hexanes (100 mL). The aqueous layer was extracted with hexanes (50 mL), and the combined organic solutions were dried ($MgSO_4$). Filtration and concentration gave the crude silyl enol ether as a clear oil.

Silyl enol ether (22a) was prepared from 0.731 g of stannane **7a** at 25 °C for 1 h affording 1.10 g of clear oil: IR (neat) 1640, 1454, 1250, 1065, 837 cm^{-1}; ^1H NMR δ 0.05–0.90 (m, 42 H), 1.20–1.60 (m, 8 H), 2.23 (m, 1 H), 2.55 (m, 1 H), 3.09 (m, 1 H), 4.04 (m, 2 H), 4.47 (d, J = 2, 1 H), 4.48 (dd, J = 4.2, 11.0, 2 H); MS m/z 526 (M^+), 469, 394, 337, 311, 285, 215.

Silyl enol ether (22b) was prepared from 0.795 g of stannane **7b** at 0 °C for 30 min affording 1.05 g of clear oil: IR (neat) 1642, 1601, 1497, 1452, 1252, 841, 777 cm^{-1}; ^1H NMR δ 0.04–0.90 (m, 39 H), 2.38 (m, 1 H), 2.64 (m, 1 H), 3.26 (m, 1 H), 3.94 (m, 2 H), 4.14 (m, 1 H), 4.58 (m, 2 H), 5.66 (m, 1 H), 5.86 (m, 1 H), 7.00 (m, 3 H), 7.38 (m, 2 H); MS m/z 562 (M^+), 547, 505, 455.

Alkylation of Silyl Enol Ethers. General. A 50-mL flask containing the crude enol ether (1.00 mmol) dissolved in 10 mL of dry THF and a magnetic stirring bar was vacuum purged with nitrogen and placed in a cooling bath at −23 °C. This solution was treated with methyllithium (1.10 mL, 1.4 M, 1.54 mmol) added at once. Stirring continued for 13 min when the yellow solution was immediately cooled to −70 °C and treated with the appropriate freshly prepared triflate solution (1.70 mmol) added over 1 min *via* cannula. The resulting solution was stirred for 5 min at −42 °C and then quenched by the addition of saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The mixture was poured into saturated aqueous ammonium chloride solution (30 mL) and extracted with diethyl ether (100 mL). The organic solution was washed with brine, dried ($MgSO_4$), and concentrated affording the crude product.

(−)-4,5-Didehydro-11,15-*O*-bis(*tert*-butyldimethylsilyl)-PGE$_2$, methyl ester (4) was obtained from enol ether **22a** and triflate **9c** as a clear oil. TLC (7:93 ethyl acetate/hexanes) R_f = 0.27. The crude material was chromatographed on 50 g of silica (20:1 hexane–ethyl acetate) affording 0.277 g of **4** as a colorless oil (47%): IR (neat) 1746, 1252, 837, 775 cm^{-1}; $[\alpha]^{25}_D$ −68.5 (*c* 0.41, CH_3OH); ^1H NMR δ 0.05 (s, 12 H), 0.89 (m, 21 H), 1.21–1.38 (m, 6 H), 1.40–1.44 (m, 2 H), 2.02–2.10 (quint, 2 H, J = 5.4), 2.17 (dd, 2 H, J = 18.2, 8.0), 2.28 (m, 2 H), 2.41 (t, 2 H, J = 8.0), 2.55–2.68 (m, 2 H), 3.66 (s, 3 H), 4.09 (m, 2 H), 5.04–5.17 (m, 2 H), 5.57 (m, 2 H); ^{13}C NMR δ −4.7 (2 C), −4.6 (2 C), 14.0, 18.0, 18.2, 22.6, 23.7, 25.1, 25.8 (3 C), 25.9 (3 C), 26.9, 31.8, 33.2, 38.5, 47.6, 51.5, 52.2, 53.6, 72.3, 72.7, 88.9, 90.2, 128.4, 136.8, 173.4, 204.7, 215.2; MS, m/z 592 (M^+), 535, 503, 460, 403; HRMS m/z calcd for $C_{33}H_{60}O_5Si_2$ (M^+) 592.3979, found 592.3995. Anal. Calcd for $C_{33}H_{60}O_5Si_2$: C, 66.84; H, 10.20. Found: C, 66.46; H, 9.91.

11,15-Bis[(*tert*-butyldimethylsilyl)oxy]-9-oxo-16-phenoxy-17,18,19,20-tetranorprost-5-yn-13(*t*)-enoic Acid, Methyl Ester (5). Obtained from racemic enol ether **22b** and triflate **8b** as a clear oil. TLC (15:85 ethyl acetate/hexanes) R_f = 0.35. The crude material was purified by chromatography on 50 g of silica (20:1 hexanes–ethyl acetate) affording 0.350 g as a colorless oil (56%): IR (neat) 1742, 1601, 1248, 837, 779 cm^{-1}; ^1H NMR δ 0.06 (s, 6 H), 0.10 (s, 6 H), 0.89 (s, 9 H), 0.91 (s, 9 H), 1.78 (quint, 2 H, J = 7.5), 2.05 (m, 1 H), 2.16–2.34 (m, 4 H), 2.41 (t, 2 H, J = 7.5), 2.67 (m, 2 H), 2.81 (m, 1 H), 3.66 (s, 3 H), 3.86 (m, 2 H), 4.11 (m, 1 H), 4.56 (m, 1 H), 5.76 (m, 2 H), 6.84–7.31 (m, 5 H); ^{13}C NMR δ −4.6 (2 C), −4.5 (2 C), 16.6, 18.2, 18.3, 24.1, 25.8 (3 C), 25.9 (3 C), 26.3, 32.8, 47.7, 51.5, 52.2, 53.0, 71.2, 71.9, 72.7, 77.3, 81.0, 114.4 (2 C), 120.7, 129.4 (2 C), 130.6, 133.1, 158.7, 173.6, 213.4; MS m/z 571 ($M^+ - C_4H_9$), 535, 457, 439, 389, 275; HRMS m/z calcd for $C_{31}H_{47}O_6Si_2$ ($M^+ - C_4H_9$) 571.2911, found 571.2913. Anal. Calcd for $C_{35}H_{56}O_6Si_2$: C, 66.83; H, 8.97. Found: C, 67.20; H, 9.19.

(−)-11α,15α-Bis[(*tert*-butyldimethylsilyl)oxy]-9-oxo-16-phenoxy-17,18,19,20-tetranorprosta-4,5,13(*t*)-trienoic Acid, Methyl Ester (24). Obtained from enol ether **22b** and triflate **9c** as a clear oil. TLC (15:85 ethyl acetate–hexanes) R_f = 0.45. The crude material was purified by chromatography on 50 g of silica (6.5:93.5 ethyl acetate–hexanes) affording 0.455 g of semipure material. Further purification was achieved by radial chromatography on silica gel using 25:75 ethyl acetate–hexanes as eluant affording 0.352 g as a clear oil (56%): IR (neat) 1963, 1744, 1601, 1250, 837, 777 cm^{-1}; $[\alpha]^{25}_D$ −79.4 (*c* 0.31, CH_3OH); ^1H NMR 0.04 (s, 6 H), 0.08 (s, 6 H), 0.86 (s, 9 H), 0.89 (s, 9 H), 2.07–2.44 (m, 8 H), 2.65 (m, 2 H), 3.66 (s, 3 h), 3.93 (dd, 2H, J = 7.4, 9.4), 4.16 (m, 1 H), 4.56 (m, 1 H), 5.04–5.15 (m, 2 H), 5.75–5.84 (m, 2 H), 6.91–7.31 (m, 5 H); ^{13}C NMR δ −4.6 (2 C), −4.5 (2 C), 18.0, 18.3, 23.7, 25.8 (3 C), 25.9 (3 C), 26.6, 33.1, 47.5, 51.5, 52.6, 53.8, 71.2, 72.2, 73.0, 88.9, 90.2, 114.4, 120.7 (2 C), 129.5 (2 C), 131.0, 133.0, 158.7, 173.2, 204.7, 214.7; MS m/z 628 (M^+), 571, 539, 521, 496, 465, 439, 389. Anal. Calcd for $C_{35}H_{56}O_6Si_2$: C, 66.83; H, 8.97. Found: C, 67.13; H, 9.27.

Diastereomeric Mixture of 24–27. Obtained from racemic enol ether **22b** and triflate **9c** as described above for the pure isomer **24**. Purification afforded 0.430 g (68%) as an oil which was a single spot on TLC. The presence of four diastereoisomers, in roughly equal proportions, was detected by ^{13}C NMR spectroscopy using peak intensities for the following resolved signals: δ 53.38, 53.44, 53.63, 53.66 (d, C12); 71.03, 71.07, 71.64, 71.67, (d, C15); 130.89, 130.95, 130.99, 131.19 (d, C13). A portion of the above mixture was desilylated as described for **1** below. The products were resolved into two diastereomeric pairs by TLC [90:10 ethyl acetate–hexanes, R_f (products) = 0.30 and 0.44]. The presence of four diastereoisomers, in roughly equal proportions, was confirmed by ^{13}C NMR spectroscopy using peak intensities for the following resolved signals: δ 53.24, 53.32, 53.90, 53.93 (d, C12); 71.28, 71.38, 71.42, 71.52 (d, C15); 131.67, 131.72, 131.78, 131.88 (d, C13). The presence of four diastereoisomers, in approximately a 3:3:2:2 ratio with RS-86505-007 and RS-86812-008 predominating, was determined by HPLC using authenic RS-86505-007 and RS-86812-008 as standards: HPLC (t_R, % area) **27** (18.4 min, 18.4), **26** (19.4 min, 20.4), **24** (32.3 min, 30.1), **25** (34.7 min, 31.2).

(−)-11α,15α-Dihydroxy-9-oxo-16-phenoxy-17,18,19,20-tetranorprosta-4,5,13(*t*)-trienoic Acid, Methyl Ester (1). To a solution of silyl ether **24** (0.385 g, 0.612 mmol) in 22 mL of acetonitrile at 0 °C was added 0.75 mL of pyridine followed by 2.2 mL of 48% aqueous HF. The cooling bath was removed and stirring continued for 3 h. Solid $NaHCO_3$ was added, and the mixture was thoroughly extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to an oily residue which was purified by radial chromatography using ethyl acetate as eluant affording 0.163 g (67%) of **1** as an oil which solidified upon standing. Recrystallization (isopropyl acetate/hexanes) gave short white needles: mp = 69–70 °C; IR (KBr) 3414 (br), 1964, 1740, 1599, 1250, 883, 758 cm^{-1}; $[\alpha]^{25}_D$ −121 (*c* 0.48, CH_3OH); ^1H NMR δ 2.15–2.45 (m, 8 H), 2.53–2.67 (m, 1 H), 2.77 (dd, 1 H, J = 6.5, 2.5), 3.02 (br d, 2 H, J = 3.0), 3.66 (s, 3 H), 3.89–4.08 (m, 2 H), 4.10–4.23 (m, 1 H), 4.52–4.62 (m, 1 h), 5.00–5.18 (m, 2 H), 5.70–5.90 (m, 2 H), 6.89–7.04 (m, 3 H), 7.26–7.36 (m, 2 H); ^{13}C NMR δ 23.7, 26.7, 33.1, 46.0, 51.6, 53.3, 54.1, 70.8, 71.6, 72.0, 88.7, 90.4, 114.6 (2 C), 121.4, 129.6 (2 C), 131.9, 133.1, 158.4, 173.5, 204.9, 213.6; MS m/z 400 (M^+) 382, 289, 275, 107, 77. Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.14; H, 7.05.