7.7–7.2 (m, 10 H), 4.4 (s, 2 H), 3.45 (bd, 2 H), 3.1 (bt, 2 H), 2.5 (bd, 2 H), 2.05 (bt, 2 H); ^{13}C NMR (DMSO-d_6) 157.0, 137.4, 131.3, 130.7, 129.9, 129.5, 129.3, 128.9, 119.0, 97.7, 58.4, 53.4, 48.4, 32.0. Anal. Calcd for $C_{20}H_{21}ClN_4O_3S\cdot H_2O$: C, 53.4; H, 5.1; N, 12.4; S, 7.1. Found: C, 53.8; H, 5.1; N, 12.4; S, 7.0. To this solid is added 1 N HCl (1 L), and the resulting mixture is refluxed for 1 h and then cooled to 0 °C. To the chilled solution is added 5 N NaOH with stirring until a pH of 5.5 is reached, whereupon precipitation of a solid occurs. The solid is filtered, washed with ether, and dried in a vacuum oven to give **8**: yield 64.5 g (60%); mp 290 °C dec. An analytical sample is prepared by recrystallizing the solid from methanol: mp 259–260 °C; ^{1}H NMR (CD_3OD) δ 7.40–7.14 (m, 10 H), 4.22 (s, 2 H), 3.62–3.54 (bt, 2 H, J = 12.3 Hz), 3.36–3.32 (bd, 2 H, J = 11.5 Hz), 2.29–2.2 (bd, 2 H, J = 14.4 Hz), 2.17–1.95 (bt, 2 H, J = 13.4 Hz); ^{13}C NMR δ 176.1, 155.0, 133.1, 130.9, 129.7, 129.69, 129.5, 128.9, 60.6, 58.8, 47.4, 28.5. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.6; H, 6.3; N, 12.5. Found: C, 71.7; H, 6.3; N, 12.6.

Sodium 4-Carboxy-4-(phenylamino)-*N*-benzylpiperidine (5). In a 340-mL capacity sealed bomb reactor equipped with a mechanical stirrer is added **8** (64.0 g, 0.19 mol), sodium hydroxide (46.0 g, 1.15 mol), and water (150 mL). The vessel is heated at 225 °C with stirring for 18$^1/_2$ h. The reaction mixture is then cooled to 0 °C, the resultant mixture is filtered, and the solid obtained is dried in a vacuum oven to give **5**: yield 52 g (82%); mp >300 °C; ^{1}H NMR (CD_3OD) δ 6.99–6.89 (m, 5 H), 6.71–6.66 (m, 2 H), 6.65–6.31 (m, 2 H), 6.24–6.19 (m, 1 H), 3.16 (s, 2 H), 1.67–1.56 (m, 2 H); ^{13}C NMR δ 183.0, 147.7, 138.5, 130.8, 129.5, 129.2, 128.3, 117.8, 116.2, 64.2, 59.9, 50.5.

***N*-Benzyl-4-anilino-4-(methoxycarbonyl)piperidine (6).** To a mechanically stirred solution of **5** (52.0 g, 0.157 mol) in dimethylformamide (600 mL) at 90 °C is added methyl iodide (10.7 mL, 0.172 mol) dropwise over a 5-min period. After the addition is complete the reaction mixture is allowed to cool to room temperature and diluted with water (600 mL). The resulting cloudy suspension is extracted with hexane (3 × 300 mL), and the combined organics is dried ($MgSO_4$), filtered, and concentrated to give pure **6** as an oil: yield 29.51 g (58%); ^{1}H NMR ($CDCl_3$) δ 7.21–7.14 (m, 5 H), 7.06–7.01 (t, 2 H, J = 8.7 Hz), 6.66–6.62 (t, 1 H, J = 7.4 Hz), 6.48–6.45 (d, 2 H, J = 9 Hz), 3.78 (s, 1 H), 3.56 (5, 3 H), 3.4 (s, 2 H), 2.52–2.46 (m, 2 H), 2.34–2.26 (bt, 2 H, J = 10.8 Hz), 2.2–2.08 (m, 2 H), 1.94–1.90 (bd, 2 H, J = 13.8 Hz); ^{13}C NMR δ 175.8, 144.8, 138.2, 128.9, 128.8, 128.1, 126.9, 118.4, 115.1, 62.8, 58.1, 52.1, 48.8, 32.9.

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An Expedient Triply Convergent Synthesis of Prostaglandins[1]

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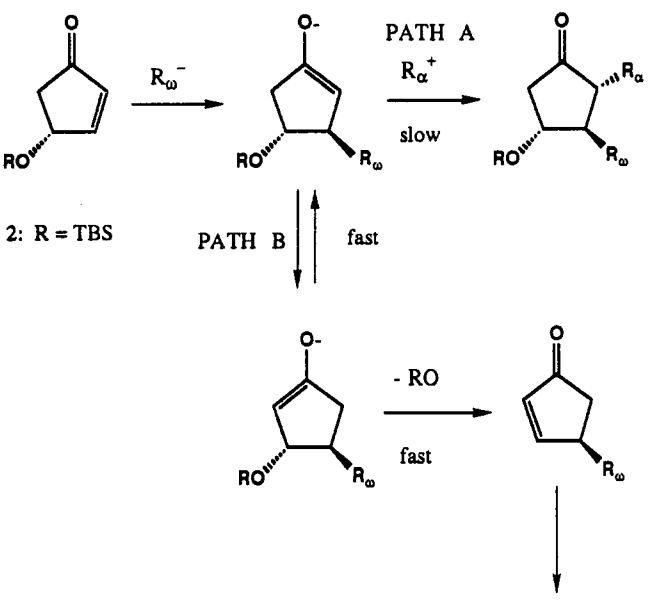
The potentially most direct and flexible route to prostaglandins (PGs) is the triply convergent approach[2] wherein the entire PG framework is assembled by tandem alkylation[3] of optically active 4-oxygenated 2-cyclopentenone derivatives (Scheme I, path A). Exploitation

Scheme I



of this methodology has, however, been impeded by the inability to directly alkylate[4] the regiochemically defined enolate, formed by organocopper-mediated conjugate addition of the ω side chain with alkyl halides.[5,6] It has been postulated[7] that enolate alkylation is slow relative to the equilibration/elimination pathway leading primarily to decomposition products (Scheme I, path B). Noyori et al.[8] have overcome this problem by transmetalation to a more stable tin enolate, thereby reducing its basicity and retarding the equilibration. The tin enolate was then alkylated with a 5-fold excess of α side chain iodide in the presence of HMPA (−30 °C, 20 h), giving PG derivatives stereoselectively in excellent yield. Johnson and Penning[9] circumvented the equilibration problem by starting with the acetonide of 4,5-dihydroxy-2-cyclopenten-1-one. The presence of the additional oxygen group constrained in a 5-membered ring inhibited equilibration by a combination of charge repulsion and angle strain. Alkylation of the enolate with alkyl iodides in the presence of HMPA (−30 °C, 3 h) gave the desired oxygenated PG derivatives along with varying amounts of cis-alkylated products. Chromatographic separation, deprotection, and selective deoxygenation afforded PGE_2 methyl ester in good yield.

This paper describes a new solution to the problem which employs a highly electrophilic α side chain trifluoromethanesulfonate (triflate)[10] to alkylate a pure lithium enolate. The use of the more reactive lithium

(1) Contribution No. 800 from the Institute of Organic Chemistry, Syntex Research.

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

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(7) See ref 2 and those cited therein.

(8) (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718. (c) For a modification using organozinc chemistry, see: Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785. (d) For an application to the synthesis of 4,5-allenyl PG's, see: Patterson, J. W., submitted.

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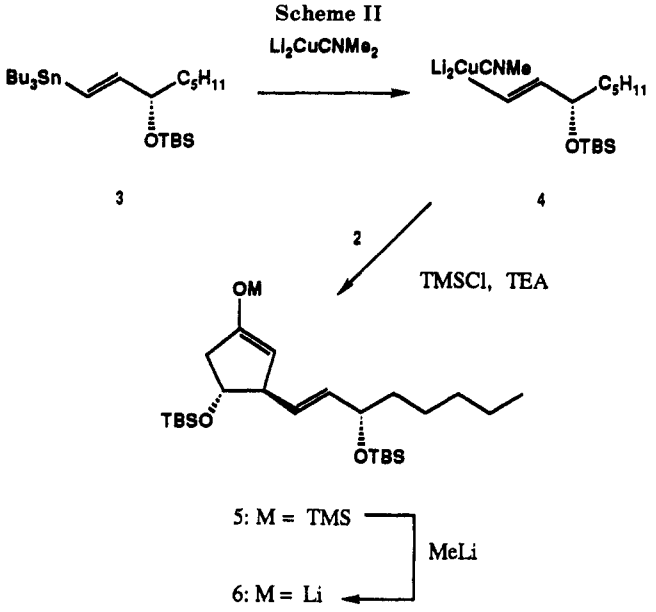
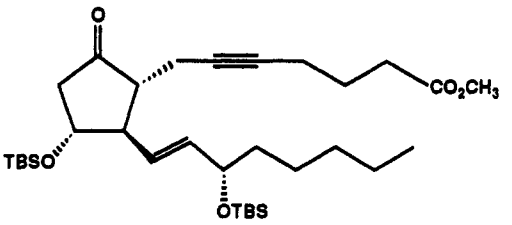
0022-3263/90/1955-4209$02.50/0

Scheme II



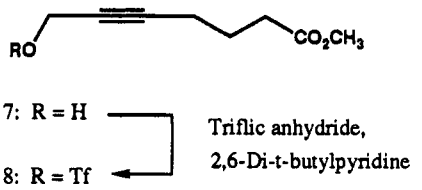
enolate in conjunction with alkylation by the extremely reactive triflate gave complete reaction within minutes, apparently faster than significant equilibration could occur. Attempts to directly alkylate either the conjugate addition adduct (copper enolate) or the tin enolate[8] in the presence of HMPA with as much as a 5-fold excess of the triflate were unsuccessful, illustrating the necessity for the more reactive lithium enolate for efficient alkylation.

The ω side chain was introduced as the mixed, higher order cuprate **4** prepared by ligand exchange[11] between $Li_2CuCNMe_2$ and vinyl stannane (**3**)[12] in THF (Scheme II). This cuprate is more easily prepared and used than the traditional phosphine-stabilized cuprates,[13] while giving equally impressive results. The unalkylated conjugate addition adduct was isolated in 92% yield following a simple proton quench with no 1,2-adducts observed in the crude reaction mixture. A solution of cuprate **4** (1.3 equiv) was cooled to −70 °C and treated sequentially with enone **2**[14] (1 equiv, 5 min), chlorotrimethylsilane (5 equiv, 15 min), and triethylamine (10 equiv, 5 min). After the mixture was warmed to 0 °C, an aqueous workup gave the crude silyl enol ether **5**[15] as a stable, clear oil.[16] The lithium enolate **6** was generated from the crude silyl enol ether[17] **5** by treatment with methyllithium (1.5 equiv) in THF (−23 °C, 13 min). The triflate **8** was prepared by the addition of a mixture of acetylenic alcohol **7**[18] (1.70 equiv) and 2,6-di-*tert*-butylpyridine[19] (1.80 equiv) to a solution of trifluoromethanesulfonic anhydride (1.78 equiv) in dichloromethane (−23 °C), 8 min).[20] An equal volume of hexane was added with cooling (−70 °C), and the mixture was rapidly filtered, affording a clear solution of the purified triflate **8**.[21]



1: TBS = t - Butyldimethylsilyl

These reactions were conducted simultaneously so that the solution of enolate **6** could be treated immediately with the solution of triflate **8** added rapidly via cannula (−70 °C). The reaction was complete by TLC in less than 5 min. Aqueous workup followed by chromatographic purification gave the desired PG derivative (**1**)[22] in 65% isolated yield. The synthesis, isolation, and purification of **1** can be conducted in 5 h on a 1-mmol scale. No evidence of polyalkylated or cis-alkylated products was observed in the crude reaction mixture. Compound **1**, an intermediate of general use in PG synthesis, has previously been efficiently converted to PGE_2, PGE_1, $PGF_{2\alpha}$, $PGF_{1\alpha}$, and PGI_2.[8b]



The method presented here offers several practical advantages over currently available technology.[8,9] It is expeditious, requiring shorter reaction times and a smaller number of expensive and/or hazardous reagents. Most notably it does not require use of the mutagenic cosolvent HMPA or a large excess of a valuable upper side chain alkylating agent which tends to complicate purification.

Experimental Section

Infrared spectra were measured on a Nicolet 5PC FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^1H and ^{13}C NMR spectra were recorded on Bruker WM 300 or AM-500 spectrometers in deuteriochloroform and are reported in ppm (δ) downfield from internal standard tetramethylsilane. Mass spectra were obtained on a MAT-311A, 112S, or CH-7 instrument. Elemental analyses were performed by the Analytical and Environmental Research group, Syntex Research. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Hexane and dichloromethane (J. T. Baker) were dried over 3A molecular sieves. Trifluoromethanesulfonic anhydride (Aldrich) was used from freshly opened ampules. Methyllithium (Aldrich) was used directly from the bottle after determining concentration by titration.[23] Optically pure (*S,E*)-3-((*tert*-bu-

(11) 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.

(12) Vinyl stannane (**3**) was prepared by the method of Corey: Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

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

(14) Enone **2** was prepared from the corresponding alcohol according to the published procedure: Takahashi, K.; Shiro, M.; Kishi, M. *J. Org. Chem.* **1988**, *53*, 3098. The alcohol (*R*)-4-hydroxy-2-cyclopentenone was obtained from Sumitomo Chemical Co.

(15) For the synthesis of a similar enol ether in the 11-deoxy-PG series, see ref 4.

(16) In addition to **5**, this mixture contained the byproduct methyltributyltin and traces of decomposition products derived from the excess cuprate, as judged by NMR spectroscopy. These impurities did not interfere with the subsequent alkylation reaction.

(17) For a review of O-silylated enolates and their use in organic synthesis, see: Rasmussen, J. K. *Synthesis* **1977**, 91. For alkylation of silyl enol ethers, see: Fleming, I. *Chimia* **1980**, *34*, 265.

(18) This material was kindly provided by Dr. John W. Patterson, Syntex Research. Casy, G.; Patterson, J. W.; Taylor, R. J. K. *Org. Synth.* **1988**, *67*, 193.

(19) Pyridine was less efficient in this reaction.

(20) 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.

(21) Attempts to isolate this themally unstable material were unsuccessful.

(22) Compound **1** gave IR, $[\alpha]_D$, ^1H NMR, ^{13}C NMR, and MS data in agreement with those reported by Noyori et al. (ref 8b).

tyldimethylsilyl)oxy]-1-(tributylstannyl)-1-octene (3) was prepared as previously described.[13] (*R*)-4-((*tert*-butyldimethylsilyl)oxy]-2-cyclopentenone (2)[14] and methyl 7-hydroxy-5-heptynoate (7)[18] were prepared as previously described. All other reagents were used as received.

Silyl Enol Ether (5). 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 high vacuum to remove any traces of water, allowed to cool, and filled with nitrogen. THF (3 mL) was added, and the suspension was cooled to 0 °C and vacuum purged with nitrogen under stirring. Methyllithium (2.00 mL, 2.80 mmol, 1.40 M) was added via syringe, and stirring continued for 15 min during which time the suspension became homogeneous. Stannane 3 (0.731 g, 1.40 mmol) dissolved in 1 mL of THF was added in one portion, and stirring continued for 60 min at 25 °C. The cuprate formation was followed by TLC in hexanes. There was a small amount of 3 left unreacted, R_f = 0.70, a large amount of demetalated alkane due to quenching, R_f = 0.57, and a small amount of unknown side product, R_f = 0.17. The resulting cuprate solution was cooled to −70 °C and treated with a solution of enone 2 (0.212 g, 1.00 mmol) in 1 mL of THF added over 1 min. After 5 min chlorotrimethylsilane (0.543 g, 5.00 mmol) was added dropwise, stirring was continued for 15 min, and triethylamine (1.01 g, 10.0 mmol) was added. The cooling bath was removed, and the mixture was allowed to warm to 0 °C when it was poured into a mixture of 50 mL of deionized water and 100 mL of hexanes. The aqueous layer was extracted with 50 mL of hexanes, and the combined organic solutions were dried over magnesium sulfate. Filtration and concentration gave a clear oil, which was taken into 50 mL of toluene and concentrated under high vacuum to give 1.10 g of 5 as a clear oil (195%). In addition to the desired enol ether 5 this material contains methyltributyltin, unreacted 3, and side products due to decomposition of the cuprate: IR (neat) 1640, 1454, 1250, 1065, 837 cm^{-1}; ^1H NMR 2.23 (m, 1 H), 2.55 (m, 1 H), 3.09 (m, 1 H), 4.04 (m, 2 H), 4.47 (d, J = 2.0 Hz, 1 H), 4.48 (dd, J = 4.2 Hz, J = 11 Hz, 2 H); MS m/z 526 (M^+), 469, 394, 337, 311, 285, 215.

5,6-Didehydro-11,15-*O*-bis(*tert*-butyldimethylsilyl)-PGE$_2$, Methyl Ester (1). The synthesis of triflate 8 (reaction A) and enolate 6 (reaction B) must be conducted simultaneously as described in dry apparatus.

Reaction A. A 25-mL flask equipped with an efficient magnetic stirring bar was charged with 3 mL of dichloromethane, cooled to −23 °C (CCl_4, solid CO_2), and vacuum purged with nitrogen. Trifluoromethanesulfonic anhydride (0.502 g, 1.78 mmol) was added with stirring followed by the dropwise addition of a mixture of alcohol 7 (0.265 g, 1.70 mmol) and di-*tert*-butylpyridine (0.344 g, 1.80 mmol) in 1.5 mL of dichloromethane over a 3-min period. The sample vial was rinsed with 0.5 mL of dichloromethane, and stirring was continued for 5 min.

Reaction B. During this 5-min period a 50-mL flask containing enol ether 5 (1.10 g, 1 mmol) dissolved in 10 mL of dry THF was vacuum purged with nitrogen and placed in a cooling bath at −23 °C.

Reaction A. After the 5-min stirring period the mixture was treated dropwise with hexanes (10 mL) and then placed in a −70 °C bath (IPA, solid CO_2) with vigorous stirring for 10 min.

Reaction B. During this 10-min period the solution was treated with methyllithium (1.10 mL, 1.54 mmol, 1.40 M), added at once with stirring. Stirring was continued for 13 min.

Reaction A. After the 10-min stirring period 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 filtrate was rinsed with 3 mL of hexanes. This flask was quickly vacuum purged with nitrogen and the clear solution was stored at (−70 °C) until used.

Reaction B. After 13 min of stirring the yellow anion solution was placed in a −70 °C bath with stirring for 4 min when the contents of the flask from reaction A was added rapidly via cannula. The resulting solution was stirred 5 min at −70 °C and 10 min at −23 °C and quenched with 5 mL of saturated aqueous ammonium chloride. After warming to ambient temperature the mixture was poured into 30 mL of saturated aqueous ammonium chloride and extracted with 100 mL of diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solution was concentrated in vacuo, and the residue was chromatographed on 50 g of silica, eluting with 5:95 ethyl acetate–hexanes. Fractions containing 1 (R_f = 0.50, 15:85 ethyl acetate–hexanes) were combined to give 0.385 g of clear oil (65%): IR (neat) 1747, 1252, 837, 775 cm^{-1}; $[\alpha]^{22}_D$ −13.3° (*c* 0.21, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.03, 0.04, and 0.05 (each s, 12 H), 0.88 (s, 18 H), 0.91 (t, 3 H, J = 6.5 Hz), 1.2–1.4 (m, 6 H) 1.45–1.60 (m, 2 H), 1.73–1.79 (quint, 2 H, J = 7.1 Hz), 2.01–2.09 (m, 1 H), 2.17–2.25 (m, 4 H), 2.39 (t, 2 H, J = 7.5 Hz), 2.65–2.76 (m, 2 H), 2.78–2.85 (m, 1 H), 3.65 (s, 3 H), 4.14 (m, 2 H), 5.48–5.64 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −4.7, −4.5 (2 C), −4.2, 13.6, 14.0, 16.8, 18.0, 18.2, 22.6, 24.2, 25.1, 25.8 (3 C), 25.9 (3 C), 31.9, 32.8, 38.5, 47.8, 51.5, 51.8, 52.9, 72.7, 73.1, 77.3, 80.9, 128.1, 136.9, 173.7, 213.9; MS m/z 592 (M^+), 577, 561, 535, 429, 403, 297; HRMS m/z calcd for $C_{29}H_{51}O_5Si_2$ ($M^+ - C_4H_9$) 535.3275, found 535.3284.

Acknowledgment. The author wishes to thank Dr. Gary F. Cooper, Dr. Colin C. Beard, and Professor E. J. Corey for helpful discussions concerning this work.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compound 1 (2 pages). Ordering information is given on any current masthead page.

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Stereospecific Vorbrüggen-like Reactions of 1,2-Anhydro Sugars. An Alternative Route to the Synthesis of Nucleosides

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Recently we described the oxidative conversion of pyranose glycals to 1,2-anhydro sugars by reaction with 3,3-dimethyldioxirane (1).[1a] While this class of compounds had been known for many years,[2] the general use of such epoxides as glycosylating agents was rather limited.[3] With the advent of a straightforward method for the stereospecific synthesis of such systems came the encouragement to investigate the effects of resident protecting groups on the efficiency of 1,2-anhydropyranohexoses as glycal donors. It was found that in the presence of nonparticipating neighboring groups, systems such as 3 undergo inversion of configuration upon reaction with various alcohols, including secondary alcohols, in the presence of zinc chloride.[1b] In the work described herein, we addressed the question as to whether 1,2-anhydro sugars might glycosylate heterocyclic bases and, if so, what would be the stereoselectivity of such reactions. Given the useful role of nonnatural nucleosides in antiviral therapy[4] the problem of providing stereospecific access to this series is of particular topical interest.

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