

Cyclization of 6 (6:5 = 92:8) was accomplished in the same manner as that as described for 5. The major products, 7 (61% GC yield) and 11, were conclusively identified by independent synthesis and spectral comparison, and the product distribution was determined by GC using the SPB-5 column. The reactions of 5 and 6 were followed by quenching aliquots of the reaction solution at 1-, 5-, 15-, and 30-min intervals and then analyzing the aliquots by GC. Characterization of the products is described above.

Cyclization of 13 (contained 10% of the trans isomer) was performed in the same manner as that described for 1a. There was predominantly one product,⁷ 75% yield, which was isolated by silica gel HPLC (solvent 80:19:1 hexane-CH₂Cl₂-CH₃CH₂OH) to give pure α -3-buten-1-yl-1,2,3,4-tetrahydro-1-naphthalenemethanol (14): ¹H NMR (CCl₄) δ 1.2-3.0 (m, 12 H), 3.5-4.0 (q, 1 H, *J* = 6 Hz), 4.7-6.1 (m, 3 H), 7.0 (s, 4 H); IR (NaCl disks) 3600-3200 (OH), 745 (s, ortho-disubstituted benzene) cm⁻¹; mass spectrum, *m/e* (relative intensity) 198 (1), 132 (100), 131 (37), 115 (19), 104 (69), 91 (41); exact mass, *m/e* calcd for TMS derivative (M⁺ - CH₃) 273.1675, found 273.1705. ¹H and ¹³C NMR spectra are provided to prove product purity.

Cyclization of 15, reaction time 30 min, gave predominantly 16 and 17 (Scheme II) in a 2:1 ratio (61% combined yield). The compounds were independently synthesized as described below.

1-Cyclohexyl-4-phenyl-1-butanone (16) was prepared by combining the Grignard reagent of 1-bromo-3-phenylpropane with freshly distilled cyclohexanecarbaldehyde and oxidation of the product by standard Jones procedures as described above for the preparation of 7. The alcohol, **4-phenyl-1-cyclohexyl-1-butanol (25)** was isolated as white crystals in 91% yield: mp 60-61 °C (recrystallized from hexane); ¹H NMR (CCl₄) δ 0.9-2.2 (m, 16 H), 2.4-2.8 (t, 2 H, *J* = 7 Hz), 3.0-3.5 (m, 1 H), 7.2 (s, 5 H); IR (Nujol mull) 3500-3100 (OH) and 750 and 690 (monosubstituted benzene) cm⁻¹; mass spectrum, *m/e* (relative intensity) 214 (13), 131 (24), 104 (100), 91 (32), and 55 (20). Anal. Calcd for C₁₆H₂₄O: C, 82.70; H, 10.41. Found: C, 82.66; H, 10.62. Oxidation of 25 on the same scale and by the same procedure as that used to prepare 7 yielded **16** (73% yield): bp 86-86.5 °C (0.02 mm); ¹H NMR (CCl₄) δ 0.9-2.1 (m, 13 H), 2.1-2.8 (m, 5 H), 7.15 (s, 5 H); IR (NaCl disks) 1710 (s, C=O), 755 and 705 (s, monosubstituted benzene) cm⁻¹; mass spectrum, *m/e* (relative intensity), 230 (50), 147 (28), 126 (44), 111 (28), 104 (78), 91 (100), 83 (55), 71 (33), 55 (88), 41 (59). Anal. Calcd for C₁₆H₂₂O: C, 83.43; H, 9.63. Found: 83.42; H, 9.74.

1-(3-Phenylpropyl)cyclohexanecarbaldehyde (17). To a solution of 100 mL of dry THF and 20.6 mL (46 mmol) of 2.22 M *n*-butyllithium was added dropwise 4.63 g (45.8 mmol) of diisopropylamine. After stirring at -70 °C for 30 min, 4.97 g (45.8 mmol) of cyclohexanecarbonitrile was added and the resulting rust-colored solution was stirred at -70 °C for 45 min. After adding 9.12 g (45.8 mmole) of 1-bromo-3-phenylpropane to the mixture, the temperature was allowed to rise to 0 °C, where it was kept for 1.25 h. After 2.5 h at room temperature, the mixture was refluxed 2 h and then stirred overnight at room temperature. The mixture was poured into 250 mL of ether and extracted twice with 5% HCl and once with saturated aqueous NaCl. After drying (MgSO₄) the organic layer was concentrated, giving 9.48 g of oil, which was estimated to be >85% pure by ¹H NMR (77% yield). Five grams of the oil was distilled, yielding 3.8 g of **1-(3-phenylpropyl)cyclohexanecarbonitrile (26)**: bp 118-121 °C (0.07 mm); ¹H NMR (CDCl₃) δ 0.9-2.1 (m, 14 H), 2.6 (t, 2 H, *J* = 7 Hz), 7.2 (s, 5 H); IR (NaCl disks) 2210 (m, CN), 750 and 700 (monosubstituted benzene) cm⁻¹; mass spectrum, *m/e* (relative intensity) 227 (45), 172 (100), and 91 (73). Anal. Calcd for C₁₆H₂₁N: C, 84.53; H, 9.31. Found: C, 84.59; H, 9.73.

To 30 mL of dry benzene was added 3.48 g (15 mmol) of **1-(3-phenylpropyl)cyclohexanecarbonitrile**. Diisobutylaluminum hydride¹⁹ (20 mL of 1 M hexane solution) was added dropwise over 22 min, and the mixture was stirred at room temperature for 2 h. The solution was carefully poured into 400 mL of 5% H₂SO₄ and then stirred for 1 h. After extracting the mixture twice with 175-mL portions of ether, the combined organic layers were washed twice with 200 mL of 5% NaHCO₃ and once with saturated aqueous NaCl and dried (MgSO₄). The concentrated organic layer was distilled, giving 1.03 g (31% yield of 17, bp 96-102 °C. Further purification of the product was accomplished by sem-

ipreparative HPLC (75:24 hexane-CH₂H₂-ethanol): ¹H NMR (CCl₄) δ 0.8-3.0 (m, 16 H), 7.2 (s, 5 H), 9.4 (s, 1 H); IR (NaCl disks) 2700 (w, CHO), 1720 (s, C=O), 715 and 760 (s, monosubstituted benzene); mass spectrum, *m/e* (relative intensity) 230 (39), 105 (26), 104 (35), 91 (100), 55 (22), 41 (21). As did 11, 17 air oxidized very fast and hence was isolated for C, H analysis as a DNP derivative, mp 137-138 °C. Anal. Calcd for C₂₂H₂₆N₄O₄: C, 64.37; H, 6.38. Found: C, 64.43; H, 6.26.

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Supplementary Material Available: ¹H and ¹³C 300-MHz NMR spectra of 1a, 4a,b, 5, 8, 14, 18b, and 23 (16 pages). Ordering information is given on any current masthead page.

A Novel Route to the 4-Anilido-4-(methoxycarbonyl)piperidine Class of Analgetics

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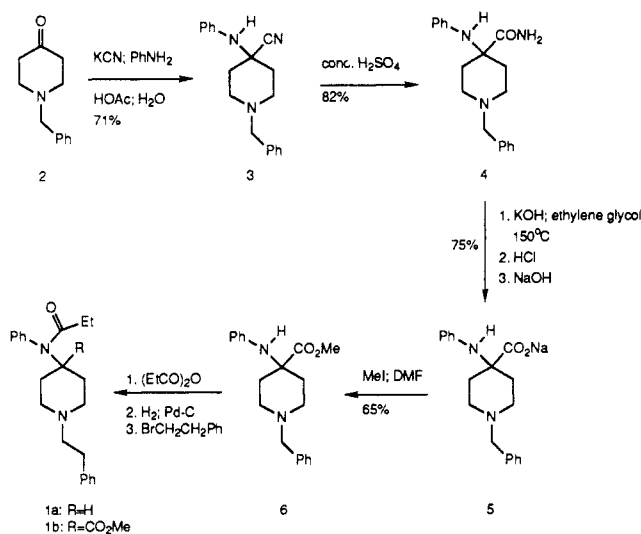
The 4-anilidopiperidine class of opioid analgetics is widely used during surgical procedures as adjuncts to anesthesia. The prototype, fentanyl (1a), was introduced in the early 1960s, and since that time research devoted to structurally modifying the piperidine ring has yielded analgetics which are much more potent and longer acting than fentanyl.¹ One such analogue, carfentanil (1b), is 27 times more potent than fentanyl and nearly 8000 times as potent as morphine in the rat tail withdrawal assay.^{1e}

The synthesis of carfentanil has been described and is depicted in Scheme I.^{1e} Upon repeating this procedure we were able to improve the yields on several steps, but all attempts at modifying the procedure in such a way that the α -amino nitrile 3 would be converted to the acid 5 directly were unsuccessful. Heating the α -amino nitrile 3 in either acid or base causes a retro-Strecker reaction. In order to avoid the stepwise hydrolysis sequence, which is complicated by the tedious isolation of the intermediate amide 4, an operationally convenient route to the methyl ester 6 was developed and is shown in Scheme II.

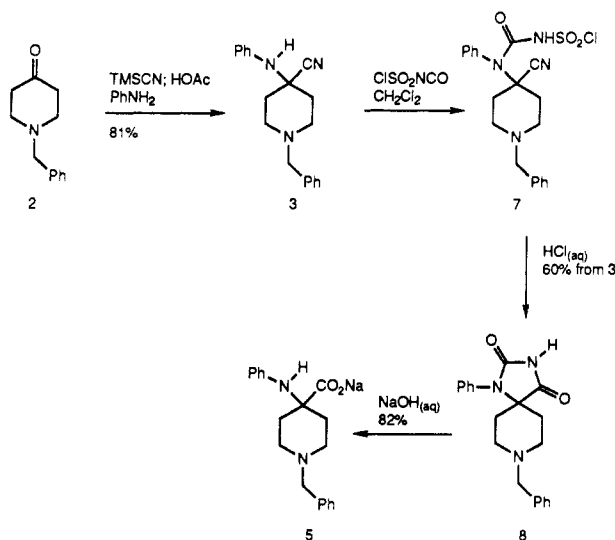
The reaction of *N*-benzyl-4-piperidinone (2) with aniline and potassium cyanide in aqueous acetic acid yielded 71% of 3. An anhydrous modification of the Strecker reaction

(1) Structure-activity relations along with references to other papers describing modifications of the 4-anilidopiperidine nucleus are given in: (a) Colapret, J. A.; Diamantidis, G.; Spencer, H. K.; Spaulding, T. C.; Rudo, F. G. *J. Med. Chem.* 1989, 32, 968. (b) Bagley, J. R.; Wynn, R. L.; Rudo, F. G.; Doorley, B. M.; Spencer, H. K.; Spaulding, T. *J. Med. Chem.* 1989, 32, 663. (c) Casey, A. F.; Huckstep, M. R. *J. Pharm. Pharmacol.* 1988, 40, 605. (d) Janssens, F.; Torremans, J.; Janssen, P. A. J. *J. Med. Chem.* 1986, 29, 2290. (e) Van Daele, P. G. H.; DeBruyn, M. F. L.; Boey, J. M.; Sanczuk, S.; Agten, J. T. M.; Janssen, P. A. J. *Arzneim.-Forsch. Drug Res.* 1976, 26, 1521. (f) Van Beaver, W. F. M.; Niemegeers, C. J. E.; Janssen, P. A. J. *J. Med. Chem.* 1974, 17, 1047. (g) Kudzma, L. V.; Severnak, S. A.; Benvenga, M. J.; Ezell, E. F.; Ossipov, M. H.; Knight, V. V.; Rudo, F. G.; Spencer, H. K.; Spaulding, T. C. *J. Med. Chem.* 1989, 32, 2534.

Scheme I



Scheme II



using aniline and trimethylsilyl cyanide (TMSCN) in glacial acetic acid was also implemented to synthesize 3 in a slightly improved yield of 81%. Although the improvement in the yield in this case using these conditions was marginal, when employing 2-fluoroaniline as the amine component in the aqueous Strecker reaction only 12% of the α -amino nitrile was isolated due to the products lability in aqueous acid. Employing the anhydrous conditions yielded 72% of the crystalline adduct. The use of TMSCN with Lewis acids to effect addition of cyanide to imines is precedented; however, we found it more efficient and convenient to use the one-pot anhydrous procedure described.^{2,3}

Reacting 3 with chlorosulfonyl isocyanate in methylene chloride at 25 °C quantitatively yielded a white solid believed to be 7 by ¹H and ¹³C NMR spectroscopy.^{4,5} Re-

fluxing 7 in 1 N HCl for 1 h followed by cooling and adjusting the pH to 5.5 caused precipitation of the desired hydantoin 8 in 60% yield. The major byproducts in this reaction were *N*-benzyl-4-piperidinone (2) and the α -amino nitrile 3. Attempts at increasing the yield of 8 by varying the acids, temperature, or concentration of the acids employed were unsuccessful.

Hydrolysis of hydantoin to α -amino acids using either strong acid or base is well documented.⁶ Heating 8 in a sealed vessel in 8 N sodium hydroxide at 225 °C for 18¹/₂ h yielded 82% of the sodium salt 5, which precipitated directly from the reaction medium upon cooling. The vigorous reaction conditions necessary to hydrolyze 8 are a manifestation of the substitution pattern of hydantoin 8. It is precedented that substituents on the N-2 (aniline nitrogen of 8) and C-5 atoms of hydantoin greatly increase their resistance to acid and alkaline hydrolysis.⁶ Indeed, all experiments aimed at converting 8 directly to 6 using NaOMe/MeOH or HCl/MeOH at temperatures ranging from reflux to 200 °C returned educt.

The carboxylate salt 5 was conveniently converted to methyl ester 6 in 50–65% yield by reacting it with methyl iodide in DMF at 90 °C.⁷ Acid-catalyzed esterification of 5 with methanol also produced 6, but the reaction is sluggish and difficult to drive to completion.

In summary, a new route to the carfentanil precursor 6 and a novel anhydrous modification of the Strecker reaction has been described. The use of the hydantoin as a latent α -amino acid allowed ready access to 6 whose conversion to carfentanil or one of its congeners is readily accomplished using literature protocols.^{1,7b}

Experimental Section

Materials were obtained from commercial suppliers and used without further purification. Melting points are uncorrected. ¹H and ¹³C NMR spectra were determined on the Varian 300 MHz spectrometer using TMS as an internal reference.

***N*-Benzyl-4-anilino-4-cyanopiperidine (3).** To a stirred solution of *N*-benzyl-4-piperidinone (100 g, 0.53 mol) and aniline (54 g, 0.58 mol) in glacial acetic acid (500 mL) is added trimethylsilyl cyanide (71 mL, 0.53 mol) dropwise over a 10-min period, maintaining the temperature below 40 °C using a cold water bath. The solution is stirred an additional 30 min and then poured into a cold ammonium hydroxide mixture (500 mL of concentrated NH₄OH, 500 g of crushed ice). Additional concentrated ammonium hydroxide is slowly added until pH 10 is reached. The resultant mixture is extracted with CHCl₃ (3 × 500 mL), and the combined organics are dried (Na₂SO₄), filtered, and concentrated to a yellow solid, which is suspended in ether (200 mL). The resulting white solid is filtered, washed with more ether, and then dried to give 3 as a solid: yield 124.7 g (81%); mp 145–146 °C; ¹H NMR (CDCl₃) δ 7.59–7.46 (m, 6 H), 7.18–7.14 (m, 4 H), 3.94 (s, 1 H), 3.8 (s, 2 H), 3.10–3.0 (bd, 2 H, *J* = 12.6 Hz), 2.75–2.66 (dd, 2 H, *J* = 11.4, 2.4 Hz), 2.6–2.54 (bd, 2 H, *J* = 12 Hz), 2.2–2.1 (dd, 2 H, *J* = 11.9, 3.3 Hz); ¹³C NMR δ 143.2, 137.9, 129.2, 128.9, 128.2, 127.1, 120.7, 120.6, 117.6, 62.5, 52.9, 49.3, 49.2, 36.0.

8-Benzyl-1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione (8). To a solution of 3 (93.2 g, 0.32 mol) in methylene chloride (1 L, dried by distilling from CaH₂) is added chlorosulfonyl isocyanate (27.8 mL, 0.32 mol) dropwise, maintaining the temperature between 20 and 30 °C with a water bath. A precipitate forms immediately. Following the addition of all of the chlorosulfonyl isocyanate, the reaction mixture is stirred an additional 30 min. Concentration of the mixture yields a white solid believed to be 7: yield 138.5 g (100%); ¹H NMR (DMSO-*d*₆) δ 11.5 (bs, 1 H),

(2) Ojima, I.; Inaba, S.; Nakatsugawa, K. *Chem. Lett.* 1975, 331.

(3) There are several other reported methods for conducting the Strecker reaction under nonaqueous conditions. (a) Harusawa, S.; Hamada, Y.; Shiori, T. *Tetrahedron Lett.* 1979, 4663. (b) Greenlee, W. J. *J. Org. Chem.* 1984, 49, 2632. (c) Mai, K.; Patil, G. *Tetrahedron Lett.* 1984, 25, 4583. (d) Mai, K.; Patil, G. *Synth. Commun.* 1985, 15, 157. (e) Hanafusa, T.; Ichihara, J.; Asida, T. *Chem. Lett.* 1987, 687.

(4) The synthesis of hydantoin from α -amino nitriles is described in: Sarges, R.; Howard, H. R., Jr.; Kelbaugh, P. R. *J. Org. Chem.* 1982, 47, 4081.

(5) Mass spectral analysis of 7 gave a spectrum similar to 8, which is consistent with 7 converting to 8 in the spectrometer.

(6) A review of the chemistry of hydantoin can be found in: Ware, E. *Chem. Rev.* 1950, 46, 403.

(7) Esters from 5 have been reported to be prepared by reacting the appropriate alkyl halide with 5 in hexamethylphosphoramide. (a) Reference 1c. (b) Janssen, P. A. J.; Van Daele, G. H. P. U.S. Patent 3,998,834, 1976.

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 $\text{C}_{20}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}\cdot\text{H}_2\text{O}$: 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; ^1H 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 $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2$: 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 $\frac{1}{2}$ 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; ^1H 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 \times 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%); ^1H 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 (s, 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 Prostaglandins¹

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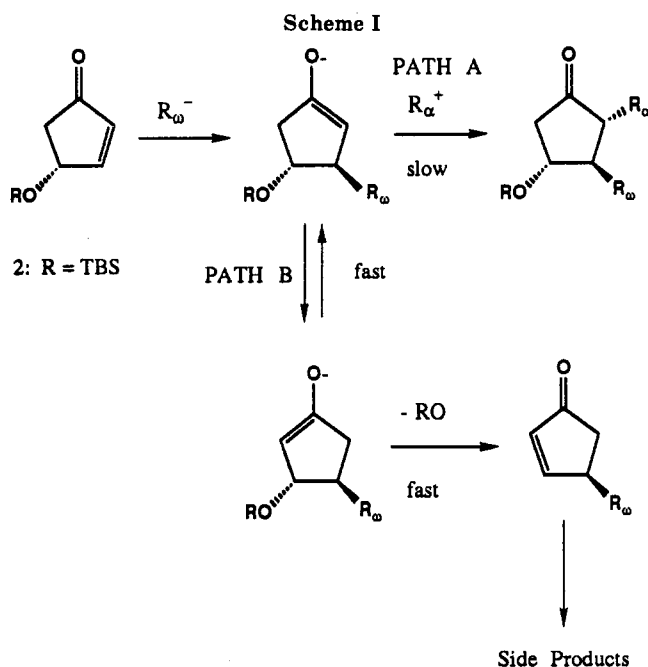
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The potentially most direct and flexible route to prostaglandins (PGs) is the triply convergent approach² wherein the entire PG framework is assembled by tandem alkylation³ of optically active 4-oxygenated 2-cyclopentenone derivatives (Scheme I, path A). Exploitation

(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.

(3) For a review of tandem alkylation of enones, see: Taylor, R. J. K. *Synthesis* 1985, 364.



of this methodology has, however, been impeded by the inability to directly alkylate⁴ the regiochemically defined enolate, formed by organocopper-mediated conjugate addition of the ω side chain with alkyl halides.^{5,6} It has been postulated⁷ 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 Penning⁹ 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 PGE₂ 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

(4) Patterson, J. W., Jr.; Fried, J. H. *J. Org. Chem.* 1974, 39, 2506.

(5) For alkylation using aldehydes, see: (a) Suzuki, M.; Kawagishi, T.; Suzuki, T.; Noyori, R. *Tetrahedron Lett.* 1982, 23, 4057. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* 1984, 25, 1383.

(6) For alkylation using nitro olefins, see: Tanaka, T.; Hazato, A.; Bannai, K.; Okamura, N.; Sigiura, S.; Manabe, K.; Toru, T.; Kurozumi, S.; Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron* 1987, 43, 813 and references cited therein.

(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.

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

(10) For a review of these powerful alkylating agents, see: Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* 1982, 85.