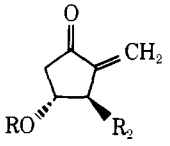
Communications to the Editor

A General Approach to Prostaglandins via Methylenecyclopentanones. Total Synthesis of (±)-Prostaglandin $F_{2\alpha}$

Sir:

Many conceptually different routes to the prostaglandins have been explored with considerable success. We now report a new approach in which methylenecyclopentanones (**1**) play a central role and illustrate it with the synthesis of (±)-$PGF_{2\alpha}$[1] from the apposite methylenecyclopentanone (cf. **9**). The synthesis of the latter also illustrates the value of the recently disclosed trapping of regiospecifically generated enolates with formaldehyde.[2]



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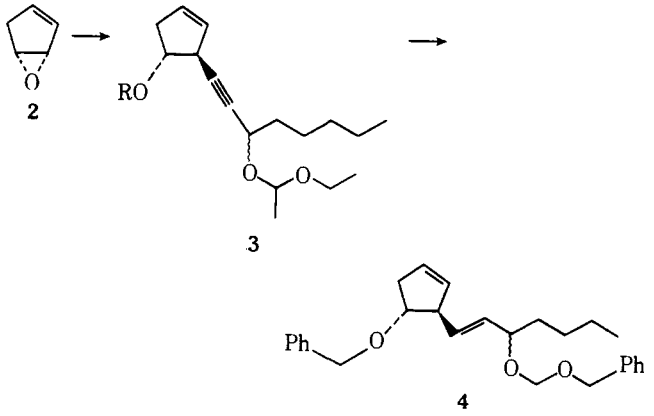
Reaction of the lithium salt of the 2-ethoxyethyl ether of 1-octyn-3-ol with 2.6 equiv of cyclopentadiene oxide[3] (**2**) (hexane, 24 hr at room temperature) gave the crude cyclopentenol **3**, R = H, in ~45% yield. This was transformed by reaction of its lithium salt with benzyl iodide (2:1 glyme-hexamethylphosphoramide, overnight at room temperature) into the benzyl ether **3**, R = benzyl (ir 2900, 1450, 1130-1080, 740, 700 cm^{-1}; NMR δ 7.32 (s, 5 H), 5.62 (m, 2 H) 4.94 (q, H_a) 4.62 (s, H_b), 435 (m, H_e, H_f), 3.51, 3.57 (q, H_g), 3.4 (b, H_h), 2.97-2.37 (m, H_i, H_j)). Conversion of **3**, R = benzyl, to the necessary protected trans vinyl carbinol was carried out by removal of the ethoxyethyl group (0.02 *N* sulfuric acid in 4.5/1 acetone-water, 60°, 1 hr), followed by reduction with lithium aluminum hydride (3.5 hr reflux with 1.5 equiv in tetrahydrofuran containing 5 equiv of sodium methoxide)[4] and, finally, treatment of the trans vinyl carbinol (ir 3350, 1450, 1120-1050, 920, 735, 700 cm^{-1}; NMR δ 7.28 (s, 5 H) 5.66-5.45 (m, 4 H), 4.53, 4.50 (s, 2 H), 3.95 (m, 2 H), 3.4 (b m, 1 H), 3.15 (b s OH) 2.7-2.35 (m, 2 H)) with 2 equiv of benzyl chloromethyl ether in excess diisopropylethylamine (overnight at room temperature) to give **4**.[5]



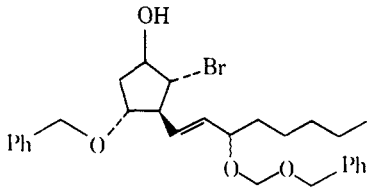
2 3 4

The bromohydrin **5** was now required as the precursor of the bromo ketone which was to serve for the generation of the necessary enolate. We hoped that addition of the elements of hypobromous acid would involve the cyclopentene double bond partly for steric reasons but especially because of the strong electron-withdrawing effect of the side chain protecting group. Regiospecificity should result from the inapplicability of the axial-equatorial description in flexible cyclopentane rings with the result that the kinetic α bromonium ion should be displaced at the less hindered site, away from the side chain.

Indeed, treatment of crude **4** with *N*-bromosuccinimide (50% excess in dimethyl sulfoxide-water (18:1))[6] gave the pure bromohydrin **5**[7] (ir 3050, 2900, 1450, 1100, 1050, 750, 700 cm^{-1}; nmr δ 7.33, 7.28 (s, 10 H), 5.64 (dd *J* = 15, 6 Hz, 1 H) 5.54 (dd, *J* = 15, 7 Hz)). The overall yield of **5** from **3**, R = benzyl, was ~50%.

Oxidation of the bromohydrin **5** (1.2 equiv of Jones reagent 0°, 2 hr under nitrogen) gave, quantitatively, the bromo ketone **6** (ir 2900, 2850, 1750, 1180, 1100, 740, 700 cm^{-1}; NMR δ 7.28, 7.26 (s, 10 H), 5.6 (H_a, dd, *J* = 15, ~5 Hz), 5.55 (H_b, dd, *J* = 15, ~5 Hz), 4.75 (H_c, q, *J* = 6.5 Hz), 4.60 (H_d, q, *J* = 6.5 Hz), 5.52 (H_e, d, *J* = 1 Hz), 4.42 (H_f, d, t, *J* = 6, 1 Hz), 4.18 (H_g, b q, *J* = 7 Hz), 4.1 (H_h, b), 2.98 (H_i, b), 2.8 (H_j, dd, *J* = 20, 7 Hz), 2.3 (H_k, ddd, *J* = 20, 6 Hz)).

The regiospecificity implied in **5** was confirmed by decoupling experiments on the bromo ketone **6** which showed that H_f is coupled with H_i.



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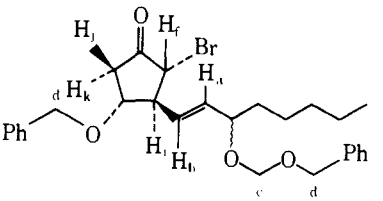

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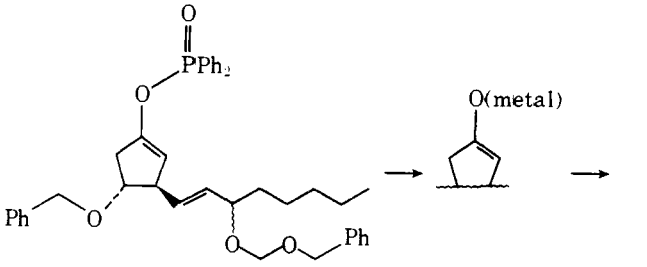
Regiospecific formation of the enolate and trapping with formaldehyde were initiated by reduction of the bromo ketone **6** with methyl diphenylphosphinite[8] (chloroform, room temperature overnight) which gave, in ~85% yield, the enol phosphinate **7** which showed,[7] inter alia, ir 1650, 1600 cm^{-1}; NMR δ 7.8-7.6 (4 H, m), 7.3-7.0 (16 H, m), 4.92 (b s, cyclopentene H), 3.1 (b s, doubly allylic H). Addition of 1.2 equiv of 2 *M tert*-butyllithium in pentane to the enol phosphinate **7** in 2:1 ether-tetrahydrofuran (−78°, 2 hr, under nitrogen), followed by 1.2 equiv of 0.35 *M* zinc chloride[9] in tetrahydrofuran, introduction of formaldehyde (−78°), and quenching with acetic acid (in the cold), gave ~80-90% yield[7] of the hydroxymethylcyclopentanone (**8**)[10] (ir 3500, 3000, 2900, 2850, 1750, 1090, 1040, 740, 690 cm^{-1}; NMR δ 7.27, 7.24 (s, 10 H), 5.55 (2 H), 4.7-4.5 (6 H)). Elimination of water was achieved by reaction with an

excess of methanesulfonyl chloride (0°, 2 hr in pyridine) and treatment of the crude, isolated, mesylate with diisopropylethylamine in ether (overnight, at room temperature) to give ~80% of the crucial methylenecyclopentanone, **9**[7] (ir 3000, 2900, 2850, 1730, 1640, 1230, 1100, 1040, 735, 700 cm^{-1}; NMR δ 7.26, 7.28 (s, 10 H), 6.10 (H_a, d, J = 3 Hz), 5.22 (H_b, dd, J = 3, 2.5 Hz), 5.71 (H_c, d, J = 15 Hz), 5.60 (H_d, dd, J = 15, 4 Hz), 4.13 (H_e, b m), 3.91, 3.89 (H_f, q, J = 7 Hz), 3.5 (H_g, b), 2.7 (H_h, dd, J = 18, 6 Hz), 2.4 (H_i, dd, J = 18, 7 Hz)). The overall yield of **9** from **5** was ~60%.



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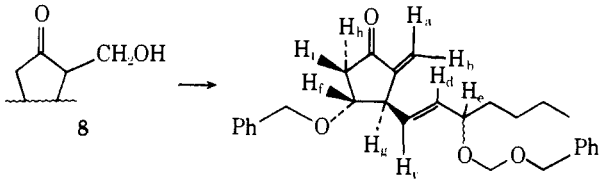

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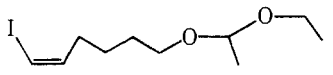
Addition of the methylenecyclopentanone, **9** (ether, −45 to −10°, 1.5 hr), to the divinyl cuprate[11] (*tert*-butyllithium, Bu_3P-CuI) from the vinyl iodide **10**[12] followed by removal of the ethoxyethyl protecting group (50% acetic acid, room temperature) and oxidation (2.4 equiv Jones reagent, 2 hr, 0°, under nitrogen) gave, in 78% yield from **9**, the cyclopentanone acid **12** (ir 3500–2400, 1745, 1710, 1200, 1080, 1060, 735, 700 cm^{-1}; NMR δ 7.33, 7.31 (10 H), 5.6–5.25 (4 H, m), 4.8–4.5 (6 H, m), 4.1 (1 H, b s), 3.8 (1 H, m)). Reduction of the cyclopentanone (tris-2-butyllithiumborohydride[13] in tetrahydrofuran, −78°), followed by removal



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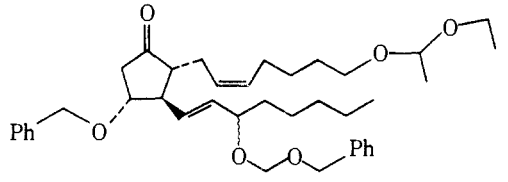

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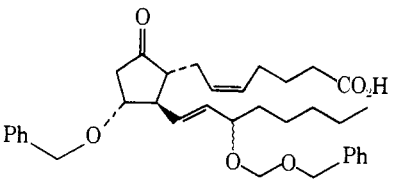
of the protecting groups with sodium (100% excess in liquid ammonia–ethanol), gave the mixture of the two C_{15} epimers of $PGF_{2\alpha}$. The more polar isomer had the same R_f as that of authentic $PGF_{2\alpha}$ (silica gel, benzene–dioxane–acetic acid, 20:20:1). The methyl esters (diazomethane) were separated by high pressure liquid chromatography (Corasil II, 100 × 1 cm column, ethyl acetate, 2 ml/min) and were thus obtained pure in 60% overall yield from the keto acid **12.** The lower retention time (24 min) C_{15} epimer was followed (36 min) by the methyl ester of (±)-$PGF_{2\alpha}$ (**13,** methyl ester), mp 66.3–67° (from hexane–ether).[14] The identity of the synthetic (±)-$PGF_{2\alpha}$ methyl ester (mass spectrum (CI, isobutane) 369 (M + 1), 351 (−18), 333 (−18 × 2), 315



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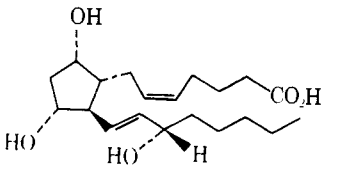

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(−18 × 3); (M + 2)/(M + 1) = 22) was confirmed by comparison of its spectral properties with those of the natural substance. In particular, the ^{13}C NMR was completely identical (for the 21 carbon atoms) with the published values.[15,16] The C_{15} epimer showed its rsonance at lower field for C_8 and C_{11} (0.6 ppm) and higher fields for C_{13} and C_{14} (1.1 and 0.6 ppm, respectively).

The success of the approach illustrated in this communication has made it possible to consider other routes (e.g., organocuprate additions to alkoxycyclopentenones) to the regiospecific enolate precursors of our 2-methylenecyclopentanones. We will describe such a sequence shortly.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

References and Notes

(1) For previous syntheses cf. (a) E. J. Corey, N. W. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969); J. Fried, C. H. Lin, J. C. Sih, P. Dalven, and G. F. Cooper, *ibid.*, **94**, 4342 (1972).
(2) G. Stork and J. D'Angelo, *J. Am. Chem. Soc.*, **96**, 7114 (1974).
(3) Cf. G. Stork, K. Utimoto, and C. Kowalski, in preparation.
(4) B. B. Molloy and K. L. Hauser, *Chem. Commun.*, 1017 (1968).
(5) The particular choice of protecting groups in **4** was critical to the success of the synthesis. They had to be quite stable to acid conditions (e.g., **5** → **6** and deprotection of the primary alcohol in **11**); the protecting group in the side chain had to be as electron-withdrawing as possible (vide infra; the benzyl ether was not good enough for the purpose) while the reverse had to be true for the ring hydroxyl to prevent its elimination with base (vide infra, **8** → **9**). Finally, both protecting groups had to be removable without harm to the allylic alcohol function.
(6) Cf. D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Am. Chem. Soc.*, **90**, 5498 (1968).
(7) Purification by chromatography on silica gel with ether–pentane.
(8) Cf. I. J. Borowitz, E. W. R. Casper, R. K. Crouch, and K. C. Yee, *J. Org. Chem.*, **37**, 3873 (1972). We found that, in contrast to enol phosphates, enol phosphinates can be cleaved at low enough temperatures to allow survival of this particular enolate.
(9) For the use of zinc chloride in aldol condensation, cf. H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Ohmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).
(10) In contrast, attempted trapping of the lithium enolate with allyl iodide at −20° gave mixtures containing ~15% of the desired alkylation product.
(11) Cf. J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970).
(12) Prepared in 78% yield (bp 88° (0.2 mm)) from the 2-ethoxyethyl ether of 5-hexynol (cf. L. I. Zakharkin, V. I. Stanko, and V. A. Bratsev, *Izv. Akad. Nauk*, 931 (1964)) by the method of A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 9256 (1972).
(13) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).
(14) Previously reported as an oil (ref 2a).
(15) W. W. Conover and J. Fried, *Proc. Nat. Acad. Sci. U.S.A.*, **71**, 2157 (1974).
(16) We thank Drs. J. Pike (Upjohn) and K. Untch (Syntex) for samples of natural $PGF_{2\alpha}$ and Mr. I. Miura for his help with the ^{13}C NMR spectra.

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