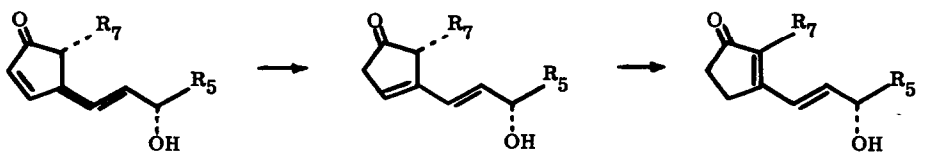
Tetrahedron Letters No. 13, pp 1161 - 1164, 1975. Pergamon Press. Printed in Great Britain.

TOTAL SYNTHESIS OF 12-METHYLPROSTAGLANDIN A_2

E. J. Corey, Christopher S. Shiner, R. P. Volante, and Clifford R. Cyr
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

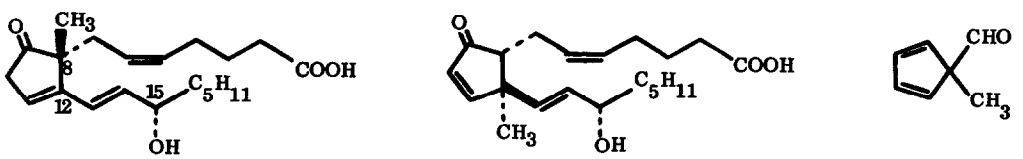
(Received in USA 21 January 1975; received in UK for publication 24 February 1975)

An important pathway for in vivo deactivation of prostaglandin A_2 is the rapid conversion in mammalian blood via PGC_2[1] to the more stable, biologically inactive PGB_2. It was anticipated that PGA



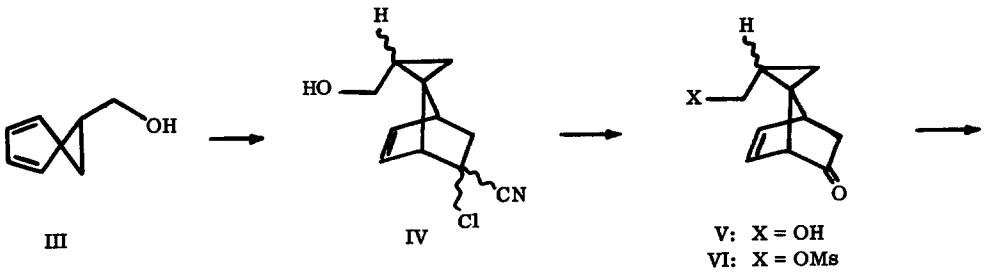
PGA PGC PGB

or PGC analogs which cannot be deactivated by transformation to PGB structures might afford more sustained biological potency. To test this possibility 8-methylPGC_2 (I) was synthesized,[2] but this substance was found to be substantially less active than PGC_2 itself. We now report the synthesis of 12-methylPGA_2 (II) by a novel extension of the bicyclo[2.2.1]heptane approach[3] to prostaglandins which

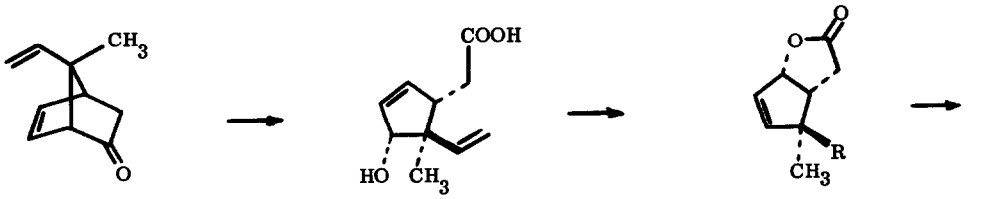


I II A

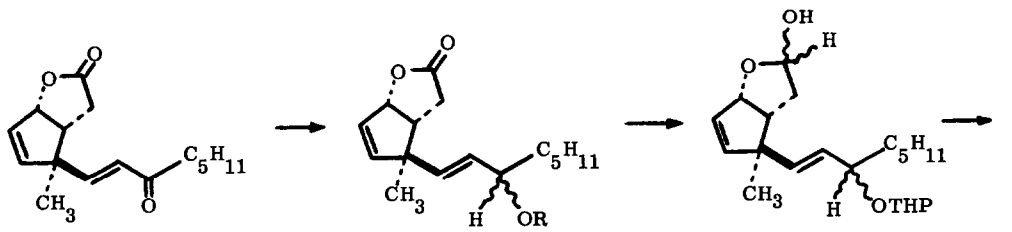
allows the stereospecific introduction of a methyl group at C-12. The application of the Diels-Alder version of the bicyclo[2.2.1]heptane approach, which requires the use of the diene A or a synthetic



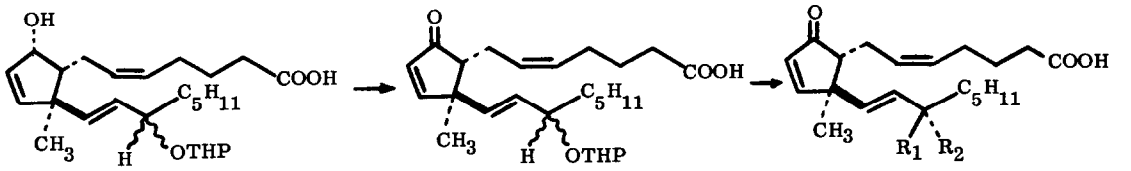
III IV V: X = OH VI: X = OMs VII: X = I



VIII IX X R = CH=CH$_2$ XI· R = CHO



XII XIII R = H XIV R = THP XV



XVI XVII II. R_1 = H, R_2 = OH XVIII R_1 = OH, R_2 = H

equivalent, is complicated by the lack of any synthetic methods for the generation of such 5,5-disubstituted cyclopentadienes. This formidable obstacle has now been overcome.

The diene III, available in quantity from the reaction of sodium cyclopentadienide with epichlorohydrin,[4] underwent Diels-Alder reaction with 2-chloroacrylonitrile (2 equiv, neat) at 25° for 12 hr, affording the adducts[5,6] IV in 98% yield. Treatment of the adducts with potassium hydroxide (2.5 equiv) in ethanol at reflux for 2.5 hr gave the hydroxyketone V (b.p. 100-105°/0.07 mm) in 66% yield after distillation. Conversion of V to the mesylate[7] VI, followed by reaction with sodium iodide (5 equiv) in acetone at 25° for 4 hr, afforded the iodide VII in 87% yield from V. Dehalogenation of VII using tributyltin hydride (1.25 equiv) and AIBN (0.03 equiv) in dry, oxygen-free benzene at 70° for 6 hr gave the pure ketone VIII in 80% yield after Kugelrohr distillation.[8] The orientation of the methyl and vinyl groups in VIII was confirmed by pmr studies using shift reagents. Baeyer-Villiger oxidation[9] of VIII with hydrogen peroxide (7.5 equiv) and sodium hydroxide (3 equiv) in aqueous methanol (1 : 1) at 0° for 12 hr afforded the hydroxy acid IX in 85% yield. The hydroxy acid could be converted to the γ-lactone X in 80% yield using boron trifluoride etherate (0.2 equiv) in methylene chloride at 0° for 3 hr. Selective cleavage of the vinyl olefinic bond in X was effected by adding solid sodium metaperiodate (1.1 equiv) in small portions over 4 hr to a solution of osmium tetroxide (0.1 equiv) and X in aqueous t-butanol (1 : 1) at 0°, giving the aldehyde XI in 55% yield (not optimized).

The aldehyde XI was readily converted to 12-methylPGA$_2$ (II) using methodology previously developed[3] for the synthesis of natural prostaglandins. Condensation of XI with the sodium salt of dimethyl 2-oxoheptylphosphonate[3] afforded the enone XII in 70% yield after chromatography. Reduction with sodium borohydride (2 mole equiv) in ethanol at -40° for 4 hr gave in quantitative yield a 1 : 1 mixture of the epimeric alcohols XIII.[10] We found it convenient to complete the synthesis using mixtures of 15-epimers, since these diastereomeric intermediates were not readily separated by chromatography. Conversion of XIII to its tetrahydropyranyl derivative[3] XIV, followed by reduction with diisobutylaluminum hydride[3] (3 equiv) in toluene at -78°, afforded the lactol XV. Treatment of the lactol with the Wittig reagent derived from 5-triphenylphosphoniovalerate ion[3] (4 equiv) in dimethyl sulfoxide gave the hydroxy acid XVI. Collins oxidation (15 equiv) in methylene chloride at -23° gave the enone XVII in 56% yield overall from XIII. Removal of the tetrahydropyranyl group using acetic acid--water--tetrahydrofuran (55 : 30 : 15) at 40° for 8 hr gave a 1 · 1 mixture of 12-methylPGA$_2$ (II) and its 15-epimer XVIII (76% yield). The epimers were cleanly separated by preparative layer chromatography on 0.25 mm silica gel plates (six elutions with methylene chloride--ether--acetic acid (90 · 10 : 1)). By analogy to the tlc behavior of natural prostaglandins and their 15-epimers, the more polar isomer has tentatively been assigned the natural 15S configuration in II.[11,12]

In preliminary tests 12-methylPGA$_2$ and its 15-epimer were inactive in blood pressure lowering (in dogs) and in inhibition of gastric acid secretion (in rats).[13] We anticipate that 12-methylprosta-

glandins of the E and F series will soon be available by extension of the scheme described herein.[14]

References

1. (a) R. L. Jones, J. Lipid Res., 13, 511 (1972); (b) R. L. Jones and S. Cammock, Advan. Biol. Sci., 9, 61 (1973).
2. E. J. Corey and H. S. Sachdev, J. Amer. Chem. Soc., 95, 8483 (1973).
3. See J. S. Bindra, A. Grodski, T. K. Schaaf, and E. J. Corey, ibid., 95, 7522 (1973), and references cited therein.
4. (a) K. Bangert and V. Boekelheide, Tetrahedron Lett., 1119 (1963); (b) H. Schaltegger, Helv. Chim. Acta, 45, 1368 (1962).
5. Formation of Diels-Alder adducts in which the hydroxymethyl group is anti to the bridge bearing the chloro and cyano groups was expected due to steric interactions; cf., E. J. Corey, T. Ravindranathan, and S. Terashima, J. Amer. Chem. Soc., 93, 4326 (1971).
6. Satisfactory infrared, proton magnetic resonance, and high resolution mass spectra were obtained for the substances reported herein. All compounds are racemic.
7. R. K. Crossland and K. L. Servis, J. Org. Chem., 35, 3195 (1970).
8. Ring-opening has been observed previously in the reaction of cyclopropylcarbinyl halides with tributyltin hydride: (a) S. J. Cristol and R. V. Barbour, J. Amer. Chem. Soc., 90, 2832 (1968); (b) C. R. Warner, R. J. Strunk, and H. G. Kuivila, J. Org. Chem., 31, 3381 (1966).
9. N. M. Weinshenker and R. Stephenson, ibid., 37, 3741 (1972).
10. No 1,4-reduction of the enone unit was observed; cf., E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, J. Amer. Chem. Soc., 93, 1491 (1971).
11. N. H. Andersen, J. Lipid Res., 10, 316 (1969).
12. We are investigating the use of cmr spectroscopy in assigning C-15 stereochemistry.
13. We thank Dr. H.-J. Hess and associates of Chas. Pfizer and Co., Inc., Medical Research Laboratories for performing the biological tests.
14. We are grateful to Dr. José Darias for experimental assistance and to the National Science Foundation for partial financial support.