Additional studies of a variety of $B_5H_8^{2-}$ salts in a wide range of solvents—protic and aprotic, polar and nonpolar—are being undertaken in an attempt to identify solution-state factors that stabilize individual polytopal forms in the eight-atom family.[11]

(11) E. L. Muetterties, R. J. Wiersema, and M. F. Hawthorne, manuscript in preparation.

(12) Address correspondence to this author at the Department of Chemistry, Cornell University, Ithaca, N. Y. 14850.

E. L. Muetterties*[12]
Contribution No. 2056, Central Research Department
E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898

R. J. Wiersema, M. F. Hawthorne
Department of Chemistry, University of California
Los Angeles, California 90024

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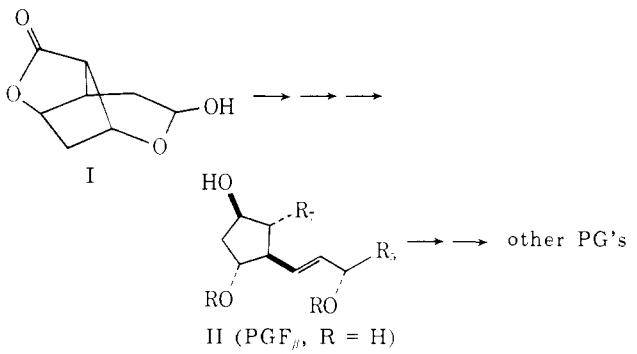
New Extensions of the Bicyclo[2.2.1]heptane Route to Prostaglandins

Sir:

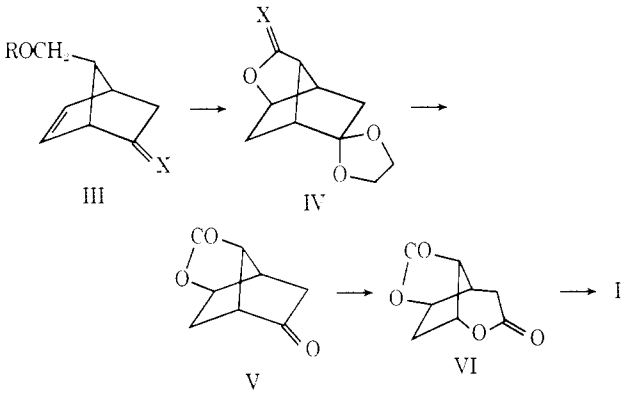
The synthetic approach to prostaglandins *via* bicyclo[2.2.1]heptane derivatives, which has previously been reported,[1] is characterized by a degree of flexibility which is unique. Not only can F_α, E, A, C, and B prostaglandins of the first, second, and third series be obtained stereoselectively and efficiently from common intermediates, but the order of synthesis can be varied (*e.g.*, F_α before E before A *or* A before E before F_α). The carboxylic side chain can be introduced before or after the 3-hydroxyoctene chain. This communication deals with the extension of the approach to allow the direct synthesis of F_β prostaglandins II specifically using the key intermediate I. Several different routes to I



have been developed with the result that this substance is now very easily available. Furthermore, as a consequence of these studies, a new mode of entry into the bicyclo[2.2.1]heptane approach to prostaglandins has been uncovered.

(1) See (a) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinschenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970); (b) E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970); (c) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971); (d) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971); (e) E. J. Corey, T. Ravindranathan, and S. Terashima, *ibid.*, **93**, 4326 (1971); (f) E. J. Corey and R. K. Varma, *ibid.*, **93**, 7319 (1971); (g) E. J. Corey, K. B. Becker, and R. K. Varma, *ibid.*, **94**, 8616 (1972); (h) E. J. Corey and T. K. Schaaf, *J. Org. Chem.*, **37**, 2921 (1972); (i) E. J. Corey, *Ann. N. Y. Acad. Sci.*, 180, 24 (1971); (j) E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, **95**, 6831 (1973); E. J. Corey and J. Mann, *ibid.*, **95**, 6832 (1973); (k) E. J. Corey and H. E. Ensley, *J. Org. Chem.*, 38, 3187 (1973); (l) for a review see J. S. Bindra and R. Bindra, *Progr. Drug Res.*, 17, 410 (1973).

The keto 2,2,2-trichloroethyl ether (III), R = CH_2CCl_3 and X = O,[1j] was ketalized with ethylene glycol–toluenesulfonic acid in benzene to give III, R = CH_2CCl_3 and X = $O(CH_2)_2O$[2,3] (96% yield), and cleaved with zinc in methanol at 30–40° to afford (90%) the hydroxy ketal III, R = H and X = $O(CH_2)_2O$.[3] This hydroxy ketal upon treatment with mercuric acetate (1 equiv) in tetrahydrofuran (THF)–water (1:1) at 25° for 15 min followed by 0.5 *M* aqueous sodium borohydride containing NaOH yielded the ether ketal IV, X = H_2 (*ca.* 70%).[3] Oxidation of this ether with 0.03 equiv of ruthenium tetroxide in the presence of aqueous sodium periodate at 25° for 10 hr followed by treatment of the product with aqueous acid gave (*ca.* 80%) the keto lactone V,[3] mp 195–196°, infrared max 5.59 and 5.69 μ ($CHCl_3$). Baeyer–Villiger oxidation of V with 1.25 equiv of *m*-chloroperbenzoic acid in methylene chloride in the presence of powdered sodium bicarbonate yielded (75%) the dilactone VI,[3] infrared max 5.57 and 5.71 μ ($CHCl_3$). Reaction of dilactone VI with 1 equiv of diisobutylaluminum hydride in toluene or methylene chloride at −78° led to selective reduction of the δ-lactone carbonyl to afford the desired γ-lactone-δ-lactol I.



A parallel synthesis of I was also developed starting from the benzyl ether[2c] III, R = $CH_2C_6H_5$ and X = O, reaction of which with acetic anhydride–boron trifluoride etherate[4] gave the acetoxy ketone III, R = AcO and X = O,[3] further converted to the above-described intermediate III, R = H and X = $O(CH_2)_2O$, by acetate cleavage (K_2CO_3–methanol) and ketalization with ethylene glycol.[5]

An even simpler synthetic route to V and I has been developed starting from norbornadiene. Reaction of norbornadiene with 1 equiv of paraformaldehyde in formic acid (97%) containing a catalytic amount of sulfuric acid at 25–30° produced diformate VII,[3] bp 104° (0.3 mm), in 84% yield.[6] Oxidation of VII with

(2) Intermediates are racemic and liquid unless otherwise indicated.

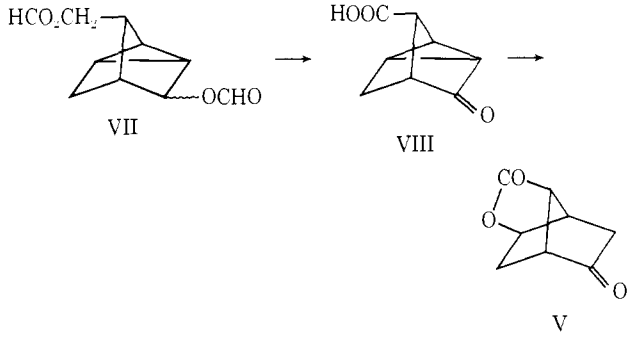
(3) Assignment of structure supported by (a) spectroscopic data (infrared, nmr) and (b) elemental analysis.

(4) E. J. Corey and P. A. Grieco, *Tetrahedron Lett.*, 107 (1972).

(5) Jones oxidation of the alcohol III, R = H and X = O, afforded the corresponding keto acid,[3] mp 120–122°, which could also be converted to the lactone V using the sequence mercuration (mercuric acetate–aqueous THF), isolation as the chloromercurial, and reductive demercuration (zinc borohydride in dimethoxyethane). However, this process is not regioselective and produces both V and the position isomeric keto lactone.

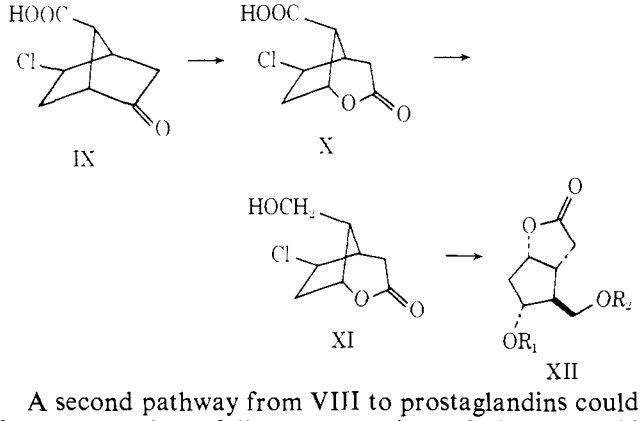
(6) The diacetate corresponding to VII can be produced similarly from norbornadiene using acetic acid–sulfuric acid as medium. For an analogous Prins reaction with rearrangement in the bicycloheptene series, see R. Zimmerman and F. Reiners, *Naturwissenschaften*, **51**, 434 (1964).

Jones reagent at 0° led directly to the keto acid VIII,[3] mp 144–145°, in 72% yield.[7] The acid VIII upon heating with 20% aqueous sulfuric acid or perchloric acid at 150° for 10 hr (or 50% aqueous acid at 150° for 1 hr) afforded the desired lactone V, mp 195–196° in 85% yield.



The optically active acid VIII was readily secured in the absolute configuration required for prostaglandin synthesis by resolution of (±)-VIII with L-(−)-α-methylbenzylamine. The optically pure salt, obtained in *ca.* 75% yield after two or three recrystallizations, had mp 154–155°, $[\alpha]^{25}D$ +59° (*c* 1, CH_3OH), and yielded the desired dextrorotatory keto acid VIII, mp 137–138°, $[\alpha]^{25}D$ +74° (*c* 1, CH_3OH). From the dextro acid VIII optically active keto lactone V, mp 195–197°, $[\alpha]^{25}D$ +266° (*c* 1, CH_3OH), was obtained as described above for the racemic form and converted to optically active dilactone VI, mp 209.5–210.5°, $[\alpha]^{25}D$ +59.7° (*c* 0.5, $CHCl_3$).

The conversion of these optically active intermediates to prostaglandins in natural optically active form can be achieved using the methods of side-chain elaboration which have already been described.[1] The details of these transformations will be reported in a separate publication.



A second pathway from VIII to prostaglandins could be developed as follows. Reaction of the (+)-acid VIII[3] with boiling aqueous hydrochloric acid (with steady introduction of gaseous HCl) for 1 hr produced cleanly (80%) the chloro acid IX,[3] mp 151–152°, $[\alpha]^{25}D$ +12° (*c* 1, CH_3OH). This was transformed cleanly by Baeyer–Villiger oxidation using *m*-chloroperbenzoic acid in methylene chloride in the presence of sodium bicarbonate (2 equiv) to the chloro lactone acid X,[3] mp 165.5–168°, $[\alpha]^{25}D$ −70° (*c* 1, in CH_3OH). The acid X was then converted in high yield to the corresponding primary alcohol XI,[3] mp 129–131°, $[\alpha]^{25}D$ −65° (*c* 1, $CHCl_3$), by sequential treatment with (1) ethyl chloroformate (1 equiv)–triethylamine (1 equiv) in ether at 0° to form the mixed anhydride and (2) ethanolic sodium borohydride at −20° or zinc borohydride in THF at 25°.

Conversion of XI to the tetrahydropyranyl ether and treatment with a mixture of 1 equiv of aqueous base, THF, and 20 equiv of 30% hydrogen peroxide as buffer produced the hydroxy lactone XII,[3] R_1 = H and R_2 = THP (80% yield), which was readily transformed into the hydroxy *p*-phenylbenzoate XII, R_1 = *p*-$C_6H_5C_6H_4CO$ and R_2 = H, mp 131°, $[\alpha]^{25}D$ −87° (*c* 1, $CHCl_3$), by acylation with *p*-phenylbenzoyl chloride–pyridine and acidic cleavage of the tetrahydropyranyl group. The hydroxy lactone ester XII, R_1 = *p*-$C_6H_5C_6H_4CO$ and R_2 = H, so obtained was identical with material which earlier had been synthesized and converted into prostaglandins.[1c]

(7) We have recently learned that Professor J. K. Sutherland of the University of Manchester, in an independent study, has also arrived at the synthesis of VIII *via* the Prins route from norbornadiene and, further, that he has succeeded in developing a route from VIII to prostaglandins which is different from those reported herein.

Jasjit S. Bindra, A. Grodski, Thomas K. Schaaf
Medical Research Laboratories, Chas. Pfizer and Company, Inc. Groton, Connecticut 06340

E. J. Corey*
Department of Chemistry, Harvard University Cambridge, Massachusetts 02138

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Solid State Conformation of the C-Terminal Tripeptide of Oxytocin, L-Pro-L-Leu-Gly-$NH_2 \cdot 0.5H_2O$

Sir:

The C-terminal tripeptide of oxytocin, L-Pro-L-Leu-Gly-NH_2 (I), has been postulated as the factor inhibiting the release of melanocyte-stimulating hormone (MSH).[1,2] Other workers,[3-6] however, have been unable to verify this proposed role for the tripeptide. Whatever its possible role as a biologically important molecule, I is experimentally and theoretically interesting in terms of molecular conformation both in isolation and in the oxytocin molecule.

Walter, *et al.*,[7] have postulated a solution conformation for I based on 300-MHz pmr studies carried out in dimethyl-d_6 sulfoxide. Based on the observed differences in chemical shift of the two N–H protons of the glycinamide moiety it was concluded that intramolecular hydrogen bonding between the trans carboxamide proton and the prolyl carbonyl oxygen results in a preferred solution structure. The basic conformational feature of the proposed solution model, a ten-membered β-turn structure, is observed in the present X-ray investigation.

I·0.5H_2O ($C_{13}H_{25}O_3N_4 \cdot 0.5H_2O$), supplied by Dr. V.

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(5) N. H. Grant, D. E. Clark, and E. I. Rosanoff, *Biochem. Biophys. Res. Commun.*, **51**, 100 (1973).
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(7) R. Walter, I. Bernal, and L. F. Johnson, "Chemistry and Biology of Peptides," Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, pp 131–135.