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A NEW SYNTHETIC ROUTE TO PROSTAGLANDINS

E. J. Corey and Barry B. Snider
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

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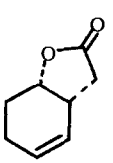
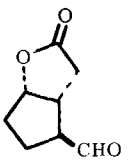
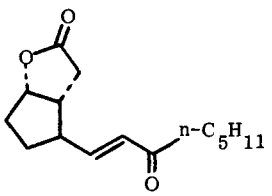
We have recently described an efficient preparation of the lactone I from 1,3-cyclohexadiene and the conversion of this substance into the aldehyde II by semi-pinacolic ring contraction using an aqueous Tl(III) reagent.[1] The aldehyde II serves as a highly attractive precursor of 11-desoxy prostaglandins which are



I



II



III

available via the enone III using processes which are now standard in the field.[2] As indicated earlier,[1] studies have continued on the extension of this approach to primary prostaglandins. This work has resulted in the route reported here which utilizes I as starting material and an allylic substitution--semi-pinacolic rearrangement sequence.

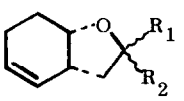
The lactone I was reduced with diisobutyl aluminum hydride in toluene for 4 hr. at -78° to afford the lactol IV[3,4] in 94% yield. Acetalization of IV was achieved by treatment with cyclohexanol and a catalytic amount of boron fluoride etherate in methylene chloride for 48 hr. at 0° to give the acetal V[4] in 91% yield. Reaction of V with 1.5 equiv. of N-phenyltriazolinedione[5] in methylene chloride for 48 hr. at 25° gave after chromatography the "ene" type product VI,[4,6] m.p. 164-165°, in 44% yield (not optimized). The reaction of N-phenyltriazolinedione with an olefin to give the corresponding allylic amine derivative represents a novel approach to the allylic functionalization of complex molecules.

Reaction of VI with osmium tetroxide in 9:1 tetrahydrofuran--pyridine gave an intractable black

solid, possibly due to interference by the acidic hydrogen on the urazole ring. To circumvent this difficulty and also to facilitate hydrolysis of the urazole ring, N-methylation of VI was carried out by addition of dimethyl sulfate (1.5 equiv.) to the sodio derivative of VI (from sodium hydride) in tetrahydrofuran (4 hr., 25°) to give VII[4,7] in 95% yield. The olefin VII was readily hydroxylated by treatment with osmium tetroxide for 6 hr. in 9:1 tetrahydrofuran--pyridine at 25° to give the diol VIII[4] in good yield.

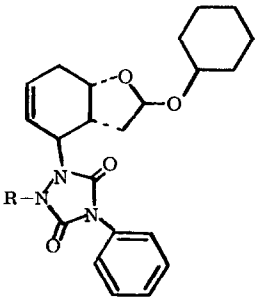
Hydrolysis of the urazole moiety in VIII was accomplished by treatment with 3 N potassium hydroxide in 3:1 methanol--water for 48 hr. at 110° in a sealed tube which had been carefully degassed to give a 93% yield of the hydrazine IX. Since this substance was readily oxidized by air to the corresponding azo compound, it was used in the next step without delay. Conversion of the hydrazine IX to the amine X was effected in 85% overall yield from VIII by hydrogenolysis over Adam's catalyst in 1% acetic acid in methanol for 24 hr. at 1 atm. and 25°.[8] Treatment of the amine with excess sodium nitrite in 25% aqueous acetic acid for 7 hr. at 0°[9] gave in 59% crude yield the aldehyde XI, which was unstable and was used immediately for the next step. Treatment of XI with the sodio derivative (from sodium hydride) of dimethyl 2-oxoheptylphosphonate[2] (1.5 equiv.) in dimethoxyethane for 2 hr. at 0° afforded after chromatography the enone XII[4] in 53% yield.

Reaction of XII with p-biphenylisocyanate in tetrahydrofuran containing triethylamine for 24 hr. at 25° gave XIII[4] in 83% yield.[10] Acetal cleavage was effected by stirring XIII in 0.2 N hydrochloric acid in 2:1 tetrahydrofuran--water for 48 hr. giving the lactol XIV[4] in 95% yield. Oxidation of XIV with Jones's reagent in acetone (5 min., -20°) gave the lactone XV[4] (85% yield) as a colorless solid, m.p. 137.5-138.5°, which was spectroscopically and chromatographically identical with material previously prepared by another route.[10] The intermediate XV has previously been converted in high yield to both $PGF_{2\alpha}$ and PGE_2.[2, 10, 11]



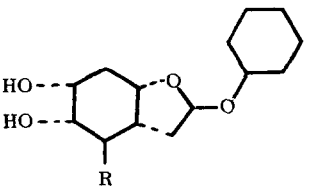
IV, $R_1 = OH$, $R_2 = H$

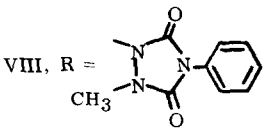
V, $R_1 = OC_6H_{11}$, $R_2 = H$



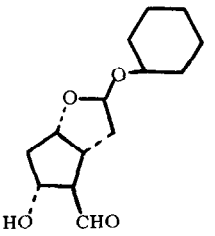
VI, R = H

VII, $R = CH_3$





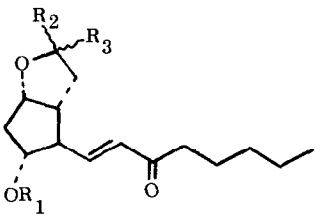
VIII, R =



XI

IX, R = $NHNHCH_3$

X, R = NH_2



XII, R_1 = H, R_2 = H, R_3 = OC_6H_{11}

XIII, R_1 = $CONHC_6H_4C_6H_5$, R_2 = H, R_3 = OC_6H_{11}

XIV, R_1 = $CONHC_6H_4C_6H_5$, R_2 = H, R_3 = OH

XV, R_1 = $CONHC_6H_4C_6H_5$, R_2, R_3 = O

References

1. E. J. Corey and T. Ravindranathan, Tetrahedron Lett., 4753 (1971).
2. See, for example, E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Amer. Chem. Soc., 91, 5675 (1969).
3. Satisfactory spectroscopic data were obtained for all intermediates.

4. Satisfactory high resolution mass spectral data were obtained for this intermediate.
5. R. C. Cookson, S. S. Gupta, I. D. R. Stevens, and C. T. Watts, Org. Syn., 51, 121 (1971).
6. For other examples of the ene reaction with 4-phenyltriazolinedione, see (a) W. H. Pirkle and J. C. Stickler, Chem. Commun., 760 (1967); (b) D. J. Pasto and A. F. Chen, Tetrahedron Lett., 713 (1973).
7. The methylated product VII was contaminated with ca. 2% of the imidate resulting from O-methylation.
8. For other examples of hydrogenolysis of hydrazines, see P. N. Rylander, Catalytic Hydrogenation over Platinum Metals, Academic Press, New York, 1967, p. 491.
9. This procedure follows one applied by Professor R. B. Woodward and coworkers to an analogous prostaglandin intermediate prepared by a different route. We thank Professor Woodward for outlining his approach to us in advance of publication.
10. E. J. Corey, K. B. Becker, and R. K. Varma, J. Amer. Chem. Soc., 94, 8616 (1972).
11. This work was assisted financially by grants from the National Science Foundation and the National Institutes of Health.