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PROSTAGLANDIN SYNTHESIS. REGIOSPECIFIC GENERATION OF A LATENT MIXED ACYLOIN UNDER NEUTRAL CONDITIONS

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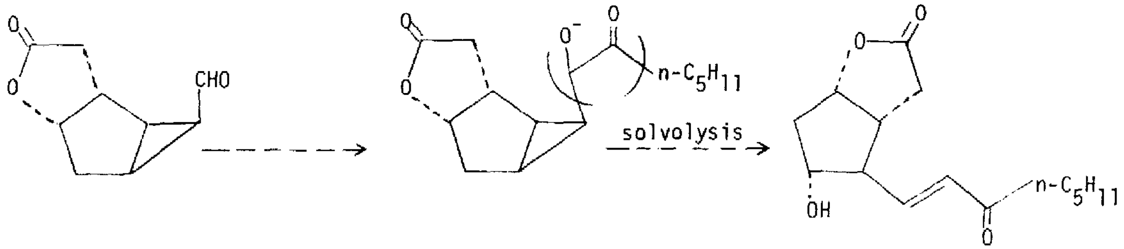
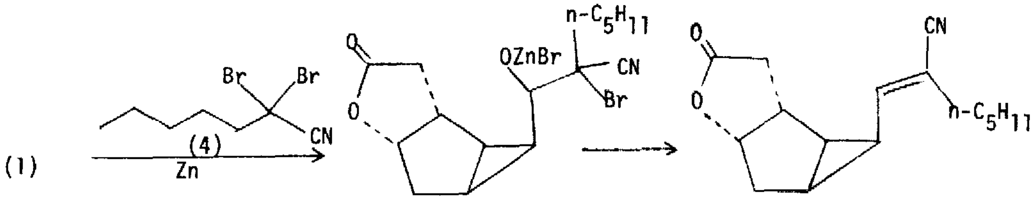
Interest in the prostaglandin intermediate (3) as a synthetic target has increased since the discovery[1] that this enone can be reduced to an allylic alcohol with high stereoselectivity. Intermediate (3) is also used for synthesis of 15-methyl prostaglandins.[2] We wish to describe a simple and efficient synthesis of enone (3).

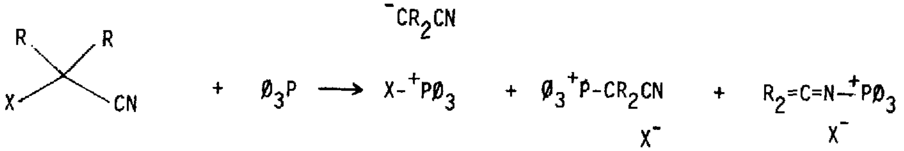


(1) (2) (3)

Resolved lactone aldehyde (1) has been prepared from norbornadiene.[3] We have addressed the problem of synthesizing a masked mixed acyloin (2) from base sensitive (1) and an acylcarbanion equivalent.[4] We anticipated that a masked acyloin (2) could be solvolyzed to a masked enone which would be converted to (3). Despite intense activity aimed toward the preparation of acylcarbanion equivalents, few[4,5,6] of these methods have been applied to the generation of masked acyloins from aliphatic aldehydes and only one[6] report claims a high yield. In these methods, strong base is used to generate acylcarbanion equivalents stoichiometrically which are subsequently allowed to add to the aldehyde. The adduct is an alkoxide (2), usually basic enough to decompose any free aldehyde in the system. In an effort to avoid these problems, we set out to (a) generate an acylcarbanion equivalent by <u>reduction in situ</u> rather than by deprotonation and to (b) trap the alkoxide (2) as formed so that the system would remain neutral. Highly successful examples of the use of reductive conditions in the presence of an alkoxide trap are known[7,8] for the formation of the C-C bond. Glycidonitriles have been formed by deprotonation of halonitriles[9,10] in the presence of ketones and by conjugate addition to α-halo acrylonitriles[11] in the presence of ketones. We hoped to maintain neutrality by reducing dihalonitrile (4)[12] in the presence of (1) under conditions favoring epoxide formation. Use of zinc[13] gave mainly (6), presumably by reductive elimination of intermediate (5). Trapping with trimethylborate or trimethylchlorosilane was not successful. Phosphines have been reported[14] to react with halonitriles to give carbanions (7) as well as C-phosphonium salts (8) and N-phosphonium salts (9) which are presumed to be formed by recombination of (7) on carbon or

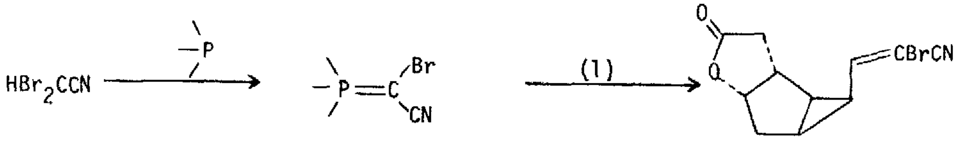


(5) (6)



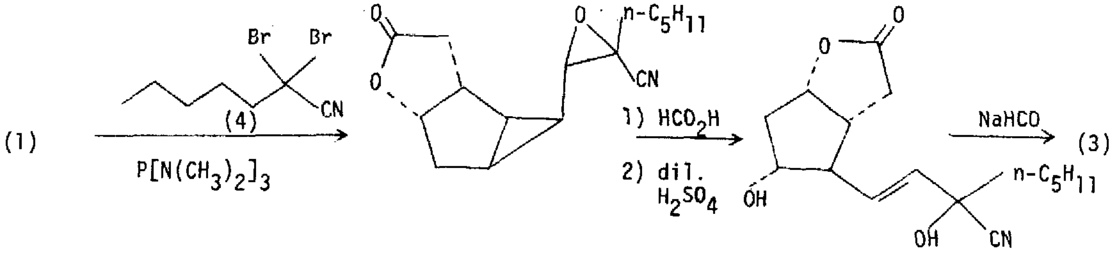
(7) (8) (9)

nitrogen, respectively. Even hindered nitriles may recombine to N-phosphonium salts (9) so that utilization of (7) could not be assured. Also, C-phosphonium salts are converted to ylids[15] and Wittig condensation could be competitive. These possibilities were realized in a model system. Reaction of dibromoacetonitrile with hexamethylphosphorous triamide[16] in the presence of (1) gave a deep red mixture from which the undesired olefin (10) was isolated in 34% yield.



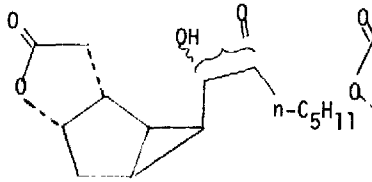
(10)

In contrast to this, use of dibromoheptanenitrile (4) under the same conditions (-15°, THF) gave (11) in 97% yield ($C_{16}H_{21}O_3N$ = 275.1521; found: 275.1522). Crude (11) was solvolyzed in formic acid[3]; concentration of the solvent and formate hydrolysis of the residue in dilute sulfuric acid gave cyanohydrin (12). The latent carbonyl of (12) was conveniently revealed by contacting an ethyl acetate solution of this material with 1N sodium bicarbonate (caution: sodium cyanide is liberated). Overall yield of (3) from lactone aldehyde (1) was 73.8% (GLC assay). The product (3) may be isolated by chromatography, or more conveniently, three stage



(11) (12)

liquid-liquid extraction using equal volumes of Skellysolve B-acetone-water purified the product so that 61% of (3) based on (1) was obtained by crystallization from tetrahydrofuran-isopropyl ether. The material was identified by comparison with authentic[17] (3). An additional 9% of (3) was recovered from mother liquor by chromatography. Side products of the sequence, arising in the solvolysis step, included four ketols (13) in 13% yield, cyclohexanols (14) in 7% yield and enone (15) in 0.6% yield. Two of the ketols were obtained in their masked form by simple opening of epoxide (11); the two other ketols were formed under deprotection conditions. (14) and (15) were obtained by alternate modes of cyclopropane ring opening.



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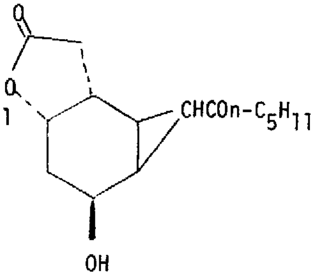

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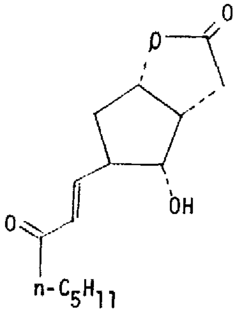

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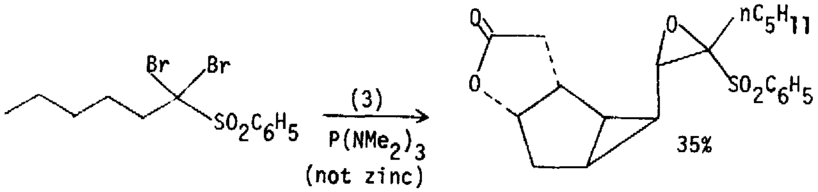

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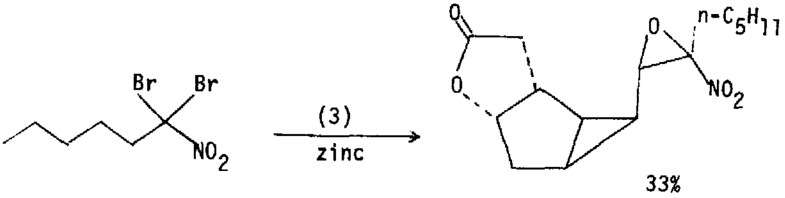

(17)

Epoxysulfone (16)[18] and nitroepoxide (17) were prepared by reduction with hexamethylphosphorous triamide and with zinc, respectively. Solvolysis of these compounds gave no olefinic products. (16) was converted to an alpha keto sulfone by sulfur migration[19], (17) appeared to suffer a similar fate.

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(12) The help of Mr. D. K. Wu in preparing 2,2-dibromoheptanenitrile is gratefully acknowledged. This material, B.P. 52-57°/10 mm, was made by modification of Stevens' monobromination conditions; C. L. Stevens and W. Holland, J.Org.Chem.,18,1112(1953).

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(17) We thank Dr. Verlan VanRheenen (Upjohn) for supplying a reference sample of hydroxyenone (3). Comparison was made with this sample by Ir, γ_{max} ($CHCl_3$) 3590-3200, 3010, 2960, 2935, 1765, 1686, 1670, 1625, 1178, 995 cm^{-1}; NMR($CDCl_3$): 401 (1, q, J=16, J=7) 370 (1, d, J=16) 297 (1, br), 245 Hz (1H, br); Uv, λ_{max} 227 (log ε 4.14); mass spectrum of the trimethylsilylether:m/e = 338, 323, 295, 281, 248, 221, 166, 145.

(18) The aid of Mr. D. K. Wu in preparing epoxysulfone (16) is greatly appreciated.

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