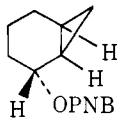
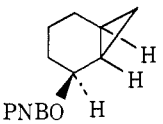
such as water and acetic acid, and the absence of **4** in the solvolysis of **13** in the presence of borohydride require that **7** and **8** be interconverting in the less nucleophilic media.

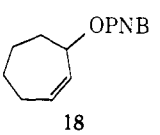
Additional evidence against the intermediacy of a bishomoantiaromatic ion, such as **9**, was provided by a kinetic study of the solvolysis of **10**, **11**, **12**, and their reduced counterparts, **16**, **17**, and **18**. As can be seen



16



17



18

from Table II, the effect of the added double bond on

Table II. Solvolysis of Saturated–Unsaturated Pairs in 70:30 v/v Acetone–Water

Compd	Temp, °C (±0.03°)	Rate, sec^{-1}	$\frac{k_{sat}}{k_{unsat}}$
10	100.0	$(3.50 \pm 0.03) \times 10^{-5}$	
16	100.0	$(6.08 \pm 0.01) \times 10^{-4}$	17
11	100.0	$(3.89 \pm 0.01) \times 10^{-5}$	
17	100.0	$(5.08 \pm 0.04) \times 10^{-4}$	13
12	120.0	$(5.49 \pm 0.03) \times 10^{-5}$	
18	120.0	$(1.02 \pm 0.01) \times 10^{-4}$	1.9

the rate of solvolysis varies from 17 for the ratio of **16** to **10** to 1.9 for the ratio of **18** to **12**. These rate decelerations are of a magnitude which might be expected due to the electron-withdrawing effect of the added double bond. Their size is far less than might be expected for a significant destabilization of the incipient carbocation as a result of bishomoantiaromaticity. Thus, no evidence for the presence of any significant effect due to bishomoantiaromaticity could be detected.

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(7) Goodyear Fellow, 1972–1973.

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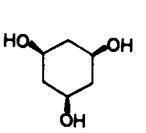
A Novel Synthesis of Prostaglandin $F_{2\alpha}$

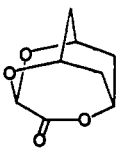
Sir:

We wish to communicate a stereospecific route to a new and versatile precursor of the prostaglandin class and its conversion to the title compound. The method described features the use of functional groups in intermediates as internal protecting agents, in a manner which at the same time serves the further purpose of providing excellent stereochemical control in the synthetic operations.

cis-Cyclohexane-1,3,5-triol (I)[1] was converted to the crystalline tricyclic lactone II[2] (mp 142–143°, yield

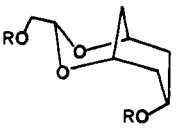


I



II

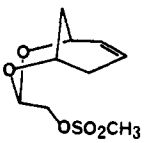
85%) by refluxing its solution in 1,2-dimethoxyethane for 30 min with an equal weight of glyoxylic acid monohydrate and an excess of Amberlyst 15.[3] Sodium borohydride reduction in absolute ethanol for 2 hr at 20° transformed II into the bicyclic diol IIIa (mp 149–



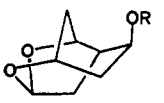
a: R=H
b: R=CH_3SO_2

III

151°, yield 97%) which in turn, when treated with 2 equiv of methanesulfonyl chloride in pyridine at −20°, yielded the dimesylate IIIb (mp 139–140°, yield 97%). When a hot suspension of the latter in either ethanol or isopropyl alcohol was mixed with a boiling solution of potassium hydroxide in the same solvent, the olefin mesylate IV (mp 54–59°, yield 89%) was formed after a brief period of reflux. When solvolyzed in boiling water–1,2-dimethoxyethane 5/1 (v/v) for 18 hr in the presence of 1 equiv of potassium carbonate, IV furnished the tricyclic carbinol Va (mp 231–238° (evacuated



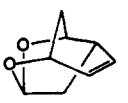
IV



V

a: R=H
b: R=CH_3SO_2

capillary), yield 70%). Va could be obtained more directly (overall yield from IIIb, 61%) by dilution of the reaction solution containing IV with aqueous potassium bicarbonate, removal of the bulk of ethanol (or isopropyl alcohol) *in vacuo*, and refluxing the resulting solution for 18 hr in a nitrogen atmosphere. With methanesulfonyl chloride and triethylamine in methylene chloride at 0°, Va afforded the crystalline mesylate Vb (mp 102–104°, yield 95%), which on boiling in isopropyl alcoholic potassium hydroxide solution for 2 hr yielded the crystalline and highly acid-sensitive tricyclic olefin VI (mp 111° (sealed capillary), yield 93%). The reagent prepared *in situ* from hydrogen peroxide, benzonitrile, and potassium bicarbonate in methanol[4] at room temperature preferentially approached the double bond of VI from the concave side of the molecule. As a result the crystalline epoxide VII was formed as the major product (mp 166–168° (sealed capillary), yield 62%). It was separated from the isomeric, less polar epoxide VIII (mp 181–182°



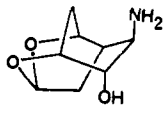
VI

VII

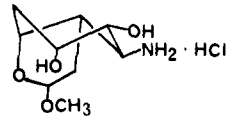
VIII

(1) H. Stetter and K. H. Steinacker, *Ber.*, **85**, 451 (1952).
(2) Elemental analytical data in excellent agreement with that calculated for the empirical formulas of all crystalline intermediates have been obtained.
(3) Supplied by Rohm and Haas Co., Philadelphia, Pa.
(4) G. B. Payne, *Tetrahedron*, **18**, 763 (1962).

(sealed capillary), yield 25%) by chromatography over basic alumina (activity IV) using petroleum ether–benzene 7/3 (v/v) and pure benzene as respective eluents for the two compounds. The undesired epoxide VIII, which is the main product when *m*-chloroperbenzoic acid (and sodium bicarbonate) is used as reagent, could be reduced quantitatively with lithium aluminum hydride in refluxing tetrahydrofuran to the carbinol Va; hence VIII by way of this reduction could be recycled. Ammonolysis of VII in 24% aqueous ammonia solution in a sealed tube at 100° for 2 hr afforded exclusively the amino alcohol IX (mp 178–180° (subliming partially above 130°), yield 90%), which when kept in a 0.33 *N* methanolic hydrogen chloride solution at room temperature was smoothly converted to the dihydroxy amino acetal hydrochloride X (mp 242–244°, yield

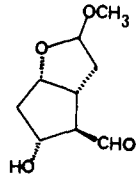


IX



X

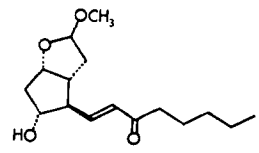
99%). In contrast to the rigid tricyclic system of IX with the amino group oriented axially, the flexible skeleton of X allows conformational change of the amino function to the equatorial position. Nmr studies on X and some derivatives showed that this change in fact did take place. Containing the function destined to serve as leaving group now properly placed in space, X was diazotized using sodium nitrite in a solution of sodium acetate in aqueous acetic acid at 0–5°. After neutralization with an aqueous sodium bicarbonate suspension, exhaustive methylene chloride extraction yielded the crude hydroxy aldehyde acetal XI, as an



XI

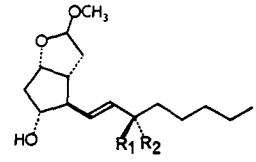
oily product (yield 80%) whose spectral properties confirmed the structure assigned. The preparation of the aldehyde XI represents a solution to the main stereochemical problem inherent in prostaglandin $F_{2\alpha}$ synthesis—the alignment of the four contiguous chiral carbon atoms in the cyclopentane moiety.

There exists precedent in the literature for the remaining transformations,[5] including the attachment of the side chains to both the free aldehyde function of XI and, later, to the aldehyde group masked erstwhile as its acetal derivative. Thus, Wittig olefination of freshly prepared XI using either 1-tributylphosphoranylidene-2-heptanone[6] or the corresponding triphenylphosphorane[7] in refluxing 1,2-dimethoxyethane afforded the unsaturated ketone XII (mp 7–10°, λ_{max} (EtOH) 231 nm (12,300), yield 79%). Reduction of XII with an excess of zinc borohydride in ether at −18°



XII

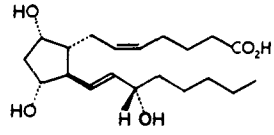
furnished an approximate 1:1 mixture of the two epimeric alcohols XIIIa and XIIIb, yield 90%. These



a: R_1 = H, R_2 = OH
b: R_1 = OH, R_2 = H

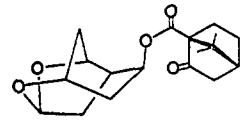
XIII

have previously been obtained *via* a different route, separated, and XIIIa transformed in two steps into *dl*-prostaglandin $F_{2\alpha}$ (XIV) by Corey and Noyori.[8,9]



XIV

When racemic Va was esterified with *S*-ketopinic acid chloride, prepared from dextrorotatory ketopinic acid,[10] $[\alpha]D^{20}$ +63° [*c* = 1 ($CHCl_3$)], by refluxing in excess thionyl chloride, a mixture of diastereomeric esters was obtained. Fractional crystallization from ethyl acetate furnished XV (mp 186–187.5°, $[\alpha]D^{20}$ −47°



XV

[*c* = 1 ($CHCl_3$)], yield 71%) as the less soluble isomer. Its saponification with potassium hydroxide in refluxing aqueous ethanol under nitrogen yielded levorotatory Va, mp 251–256° (sealed capillary), $[\alpha]D^{20}$ −149° [*c* = 1 ($CHCl_3$)], yield 95%, whose absolute stereochemical structure corresponds to the one shown.[11] Processing (−)-Va according to the scheme outlined above[12] led to natural prostaglandin $F_{2\alpha}$ (XIV) identical with authentic material in its chromatographic behavior, specific rotation,[13] and ^{13}C nmr spectrum.[14]

(5) *E.g.*, E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(6) N. Finch and J. J. Fitt, *Tetrahedron Lett.*, 4639 (1969).

(7) M. Miyano and R. C. Dorn, *J. Org. Chem.*, 37, 1818 (1972). We should like to thank Dr. Miyano for communicating his results to us prior to publication.

(8) E. J. Corey and R. Noyori, *Tetrahedron Lett.*, 311 (1970).

(9) The undesired epimer reverts to its precursor XII on oxidation with activated manganese dioxide in methylene chloride; see also ref 5.

(10) Obtained by following the procedure given by P. D. Bartlett and L. H. Knox in "Organic Syntheses," Vol. 45, W. G. Dauben, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, pp 14 and 55.

(11) The assignment was based on circular dichroism and optical rotatory dispersion data exhibited by the ketone, mp 149–150°, $[\alpha]D^{20}$ −40° [*c* = 1 ($CHCl_3$)], derived from optically active Va by chromium trioxide–pyridine oxidation in methylene chloride (positive Cotton effect).

(12) Physical data of intermediates in the natural series were as follows (rotations were taken in $CHCl_3$, *c* = 1, except as noted) (compound, mp (°C), $[\alpha]D^{20}$): Vb, *ca.* 120 (dec), −92°; VI, 108.5–114 (sealed capillary), +12° [*c* = 1.45]; VII, 169–171 (sealed capillary), −95°; IX, 176–178, −155°; X, 235–236, −117° [*c* = 0.5, MeOH]; XII, 26–27, −76°; XIIIa, wax, −71°.

(13) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

(14) G. Lukacs, F. Piriou, S. D. Gero, D. A. Van Dorp., E. W. Hagaman, and E. Wenkert, *Tetrahedron Lett.*, 515 (1973).

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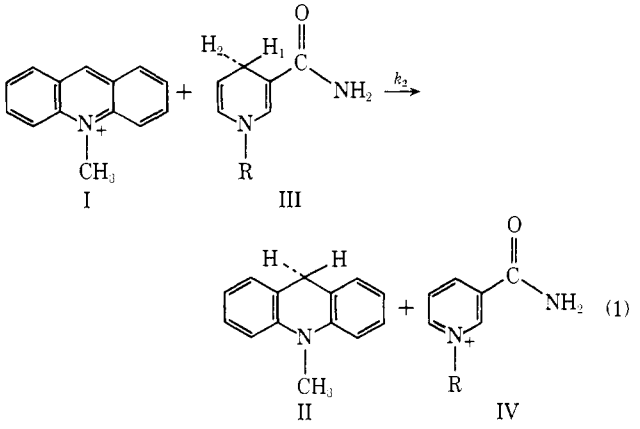
Model Dehydrogenase Reactions. Reduction of *N*-Methylacridinium Ion by Reduced Nicotinamide Adenine Dinucleotide and Its Derivatives

Sir:

Despite the central importance of NADH and NADPH in biochemical oxidation–reductions, relatively few facile nonenzymic reductions by 1,4-dihydronicotinamides are known. "Model" reactions of this type are of potential value in that they may provide helpful clues as to the mechanism of action of NAD^+- and $NADP^+$-dependent dehydrogenases.[1-9] In the present communication we wish to report a new nonenzymic reaction of dihydronicotinamides. Specifically, we have found that *N*-methylacridinium ion (I) is rapidly reduced to *N*-methylacridan (II) by β-NADH and a variety of dihydronicotinamide derivatives at room temperature in essentially quantitative yield (eq 1). Since the reverse reaction has not been observed



(1)

experimentally, the reaction must be strongly thermodynamically favored in the direction written. The reduction of *N*-methylacridinium (I) is considerably more rapid than other nonenzymic transhydrogenation reactions such as the hydrogen exchange between NAD^+ and NADH[10] and the reduction of *N*-benzyl-3-acetylpyridinium chloride[11] and the acetyl analog of NAD^+ by NADH.[12,13]

The second-order rate constants for the reduction of I by a series of dihydronicotinamides are summarized in Table I. Since II and the various oxidized nicotinamides do not absorb strongly above 320 nm, the reaction can be conveniently assayed by following either (a) the disappearance of absorption at 358 nm where I absorbs very intensely ($\epsilon = 2.6 \times 10^4\ M^{-1}\ cm^{-1}$) and the dihydronicotinamides absorb with variable intensities depending on the nature of R; (b) the disappearance of the characteristic absorbance of I in the region of 420 nm; or (c) the disappearance of the intense fluorescence of I at 490 nm. The latter two methods for assaying the reaction are particularly useful when the dihydronicotinamides are present in large excess relative to I.

Table I. Rates of Reduction of *N*-Methylacridinium Ion by a Series of Dihydronicotinamides[a]

Compound	R	k_2, M^{-1} sec^{-1}
β-NADH (IIIa)	ADPR	101.2 ± 2.4[b]
β-NADH (IIIa)	ADPR	98.2 ± 5.1[c]
β-NMNH (IIIb)	Ribose 5-phosphate	41.9 ± 1.6[b]
IIIc′	$CH_3CH_2CH_2$	2040 ± 50[d]
IIIc″	$CH_3CH_2CH_2$; $H_1 = D$	1620 ± 50[d]
IIIc‴	$CH_3CH_2CH_2$; $H_1 = H_2 = D$	1398 ± 60[e]

[a] In these experiments, the concentration of reactants did not exceed 10^{-4} *M*. Under these conditions, the reaction was strictly first order with respect to each component. [b] pH 8.0, 0.1 *M* phosphate buffer; 25°. [c] pH 7.0, 0.1 *M* phosphate buffer; 25°. [d] pH 8.4, 0.01 *M* phosphate buffer; 25°. [e] pH 8.7, 0.01 *M* phosphate buffer; 25°.

The production of II and IV was confirmed by nuclear magnetic resonance and mass spectra, ultraviolet and visible absorption spectra, and thin-layer chromatographic analysis of the products isolated from the reaction mixture. Independently prepared samples of II and the various nicotinamides were used as internal standards in these procedures. Spectral analyses of the reaction mixtures prior to isolation of the products were completely consistent with the stoichiometry indicated in eq 1.

The reaction proceeds by direct hydrogen transfer and is unaffected by reagents known to affect the rates of free-radical reactions. Direct hydrogen transfer was demonstrated in two ways. First, I was reduced with NADH in D_2O and the deuterium content of the resulting *N*-methylacridan was determined from its appearance potential mass spectrum. The intensity of the P + 1 peak (*m/e* 196) for this sample and that for II generated from the oxidation of NADH in H_2O were equal and corresponded to the intensity (15.72%) predicted from the natural isotopic abundance for a parent

(1) D. Mauzerall and F. H. Westheimer, *J. Amer. Chem. Soc.*, **77**, 2261 (1955).
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(4) D. C. Dittmer and R. A. Fouty, *J. Amer. Chem. Soc.*, **86**, 91 (1964).
(5) K. A. Schellenberg, G. W. McLean, H. C. Lipton, and P. S. Lietman, *J. Amer. Chem. Soc.*, **89**, 1948 (1967).
(6) (a) T. P. Goldstein, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 11–16, 1966, Abstract C196; (b) J. J. Steffens and D. M. Chipman, *J. Amer. Chem. Soc.*, **93**, 6694 (1971).
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(11) G. Cilento, *Arch. Biochem. Biophys.*, **88**, 352 (1960).
(12) M. J. Spiegel and G. P. Drysdale, *J. Biol. Chem.*, **235**, 2498 (1960).
(13) G. R. Drysdale, M. J. Spiegel, and P. Strittmatter, *J. Biol. Chem.*, **236**, 2323 (1961).