benzyl alcohol in methylene chloride. The allylic methyl group of Δ^2 ester **3b** could be functionalized by azobisisobutyronitrile-initiated bromination using N-bromosuccinimide in hot carbon tetrachloride. Although no attempts were made to purify this bromination product, an nmr spectrum of the crude material displayed absorptions at δ 6.48 (crude doublet; C-2 vinyl H) and 4.14 (quartet, J = 8 Hz; methylene bearing bromine), relative areas *ca.* 1:2, consistent with allylic bromide **4**. The crude allylic bromide, in which the only significant contaminant was starting material **3b**, was immediately treated with potassium acetate in acetone. The newly formed species was separated from deacetoxy starting material (*ca.* 15%) by preparative tlc and was shown to be a mixture by nmr analysis. That this product (**5**), obtained in 30–40% yield, was an equilibrium mixture of cephalosporin V *p*-methoxybenzyl ester (30%) and its Δ^2 isomer (70%) was verified by nmr comparison with an authentic mixture.[4] Although the Δ^3 ester portion of mixture **5** did not appear to be readily separable from its Δ^2 isomer by chromatographic means,[5] the total ester mixture could be cleaved with trifluoroacetic acid in benzene to give a mixture containing cephalosporin V, as indicated by tlc and bioautography of a paper chromatogram.

Oxidation with *m*-chloroperbenzoic acid[6] in chloroform smoothly converted the Δ^2,Δ^3 sulfide mixture **5** into the Δ^3 sulfoxide **6**, mp 161–163°,[2] identical with authentic sulfoxide[7] according to physical measurements and mixture melting point. This oxidation–isomerization provides a means for converting all the cephalosporin material present to the potentially biologically active Δ^3 isomer (Δ^2-cephalosporins are essentially inactive). The explanation for this convenient conversion must involve electronic considerations favoring an α,β- over β,γ-unsaturated ester system as well as an allylic over a vinylic sulfoxide.[8] Other workers[9] have been unsuccessful in attempts to oxidize the Δ^2 sulfide ester system with oxidants milder than *m*-chloroperbenzoic acid, such as periodate.

Reduction of sulfoxide **6** in DMF by acetyl chloride–sodium dithionite[10] afforded *p*-methoxybenzyl 3-acetoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate (**7a**, cephalosporin V *p*-methoxybenzyl ester),[2] mp 108–111°, in 55% yield after chromatographic purification. There was no other cephalosporin product. Cleavage of ester **7a** with trifluoroacetic acid in benzene containing some anisole gave 3-acetoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid (**7b**, cephalosporin V), identical with authentic cephalosporin V by tlc, bioassay, and nmr comparison.

(4) Prepared by treatment of *p*-methoxybenzyl 3-acetoxymethyl-7-phenoxyacetamido-2-cephem-4-carboxylate,[2] mp 110–113°, at room temperature with potassium acetate in acetone.

(5) R. B. Woodward, *et al.* [*J. Amer. Chem. Soc.*, **88**, 852 (1966)] in their synthesis of the cephalosporin system separated a similar Δ^2,Δ^3 equilibrium mixture of the trichloroethyl esters of thiopheneacetamidocephalosporanic acid by chromatography and then carried out ester cleavage to obtain the pure, biologically active Δ^3 acid.

(6) A discussion of this oxidation is in preparation by several members of this laboratory.

(7) Prepared by oxidation of *p*-methoxybenzyl 3-acetoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate with *m*-chloroperbenzoic acid in chloroform.

(8) See, for example: D. E. O'Connor and W. I. Lyness, *J. Amer. Chem. Soc.*, **86**, 3480 (1964).

(9) J. D. Cocker, S. Eardley, G. I. Gregory, M. E. Hall, and A. G. Long, *J. Chem. Soc., C*, 1142 (1966); however, they could oxidize Δ^2 sulfide acids with sodium periodate to the Δ^3 sulfoxide, with some concomitant decarboxylation.

(10) A discussion and other examples of this type of reduction will be the subject of a later paper.

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Stereo-Controlled Synthesis of Prostaglandins $F_{2\alpha}$ and E_2 (*dl*)

Sir:

This communication describes a new approach to the synthesis of prostaglandins which was designed with the following objectives in mind: (1) control of stereochemistry, (2) the synthesis of all the primary prostaglandins and a variety of analogs from a single precursor, and (3) optical resolution at an early stage.[1-3]

Addition of cyclopentadienylsodium to a slight excess of chloromethyl methyl ether in tetrahydrofuran at −55° furnished after evaporation of solvent below 0° 5-methoxymethyl-1,3-cyclopentadiene,[4,5] which was

(1) For previous papers from these laboratories on the total synthesis of the primary prostaglandins E_1 and $F_{1\alpha}$, see (a) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, **90**, 3245 (1968); (b) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968); (c) E. J. Corey, I. Vlattas, and K. Harding, *ibid.*, **91**, 535 (1969).

(2) A group at the Upjohn Co. has recently described syntheses of racemic prostaglandins E_1, E_2, and $F_{2\alpha}$; see (a) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *ibid.*, **90**, 5895 (1968); (b) U. Axen, F. H. Lincoln, and J. L. Thompson, *Chem. Commun.*, 303 (1969); (c) W. P. Schneider, *ibid.*, **304** (1969).

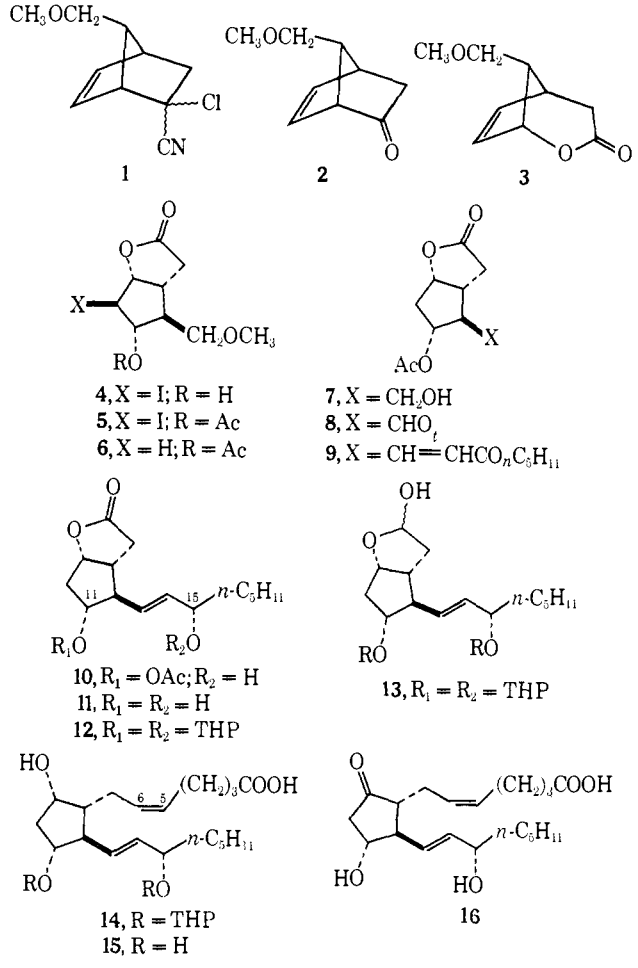
(3) For a review on prostaglandins and the definition of primary prostaglandins, see S. Bergström, *Science*, **157**, 382 (1967).

(4) G. Kresze, G. Schulz, and H. Walz, *Ann. Chem.*, **666**, 45 (1963). This product is subject to facile isomerization to 1-methoxymethyl-1,3-cyclopentadiene.

(5) Infrared and nmr (at 60 MHz) spectra were in agreement with the assigned structure.

subjected to the Diels–Alder reaction with 2-chloroacrylonitrile (5 equiv) at 0° in the presence of cupric fluoroborate as catalyst.[6] The resulting product, bp 96–99° (0.7 mm), containing a mixture of stereoisomers[5,7] differing in *exo–endo* orientation of cyano and chloro groups (**1**) (see Scheme I), was smoothly converted

Scheme I



by treatment with 2.5 equiv of potassium hydroxide (added as a hot saturated aqueous solution) in dimethyl sulfoxide for 14 hr at 25–30° to the *anti*-bicyclic ketone **2**[5,7] (80% yield), bp 64–66° (0.1 mm), homogeneous by gas chromatographic analysis.[8] Reaction of the ketone **2** with 1.25 equiv of *m*-chloroperbenzoic acid in methylene chloride in the presence of sodium bicarbonate resulted in selective Bayer–Villager oxidation to form the liquid lactone **3**[5,7] (carbonyl absorption (CCl_4) at 5.70 μ) in >95% yield. Saponification of **3** in water containing 2.5 equiv of sodium hydroxide at 0° followed by neutralization with carbon dioxide and treatment with 2.5 equiv of aqueous potassium triiodide solution at 0–5° for 12 hr produced the crystalline iodo lactone **4**[5,7] (carbonyl absorption ($CHCl_3$) at 5.61 μ, mp 87.5–88.2° (from benzene) (80%)), converted by reaction with acetic anhydride–pyridine (25°, 15 min) to the corresponding acetate **5**,[5,7] mp 99–100° (from CCl_4). Deiodination of **5** using tributyltin hydride in benzene at 25° (initiation with azobisisobutyronitrile) produced the oily acetoxy methyl ether **6**[5,7] (99% yield), which was demethylated by reaction with boron tribromide[9] (5.5 equiv) in methylene chloride at 0° to form the crystalline acetoxy alcohol **7**[5,7] (>90% yield). Oxidation of the alcohol **7** using the Collins reagent[10] in methylene chloride at 0° produced the unstable oily β-acetoxy aldehyde **8**,[5] which without purification was treated with the sodio derivative of dimethyl 2-oxoheptylphosphonate[1b] in dimethoxyethane at 25° for 1 hr to form stereospecifically the *trans*-enone lactone **9**[5,7] (70% over-all from **7**), uv max 224 nm (ϵ 9700), mp 44–46°. Treatment of the enone **9** with excess zinc borohydride in dimethoxyethane at 20° for 0.5 hr afforded in >97% yield a mixture of the 15α-hydroxy-11α-acetoxylactone **10** and the 15β epimer (ratio *ca.* 1:1).[11] Separation of the desired 15α isomer **10**[5,7] from the mixture was accomplished by preparative layer chromatography on silica gel, using ether as eluent. Further, the 15β epimer of **10** could also be utilized in the synthesis, since it reverts to the precursor **9** upon treatment with either activated manganese dioxide in methylene chloride or dichlorodicyano-*p*-benzoquinone in dioxane at 50°.[1b,1c] The direct conversion of 15-*epi*-**10** to **10** by SN2 displacement of a 15-sulfate ester,[12] potentially an even simpler operation, is currently under study.

dl-Prostaglandins $F_{2\alpha}$ and E_2 were obtained from the 15α-hydroxy-11α-acetoxylactone **10** in the following way. Deacetylation of **10** with an equimolar amount of potassium carbonate in methanol at 25° for 15 min gave the diol **11**,[5,7] which was converted into the bistetrahydropyranyl derivative **12** using dihydropyran (10 equiv) in methylene chloride containing *p*-toluenesulfonic acid (0.01 equiv) at 25° for 15 min. Reduction of **12** by means of 2 equiv of diisobutylaluminum hydride[13] in toluene at −60° for 30 min yielded the lactol **13** which was condensed with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid and sodio methylsulfinylcarbanide in dimethyl sulfoxide[14,15] to form the bistetrahydropyranyl ether of *dl*-prostaglandin $F_{2\alpha}$ (**14**)[5] (80% yield from **11**). Hydrolysis of **14** using 2:1 acetic acid–water at 37° for 3 hr afforded >90% yield of *dl*-prostaglandin $F_{2\alpha}$ (**15**) as a colorless oil (homogeneous by tlc analysis) which exhibited the same ir, nmr, and mass spectra as a sample of the natural hormone[16] and which also showed identical chromatographic behavior using silica gel (without and with silver nitrate) and several tlc solvent systems.[17] The methyl ester prepared by reaction of diazomethane

(6) Cupric ion accelerates the Diels–Alder addition and allows the reaction to proceed at 0° in >90% yield without appreciable concurrent isomerization of 5-methoxymethyl-1,3-cyclopentadiene to 1-methoxymethyl-1,3-cyclopentadiene.

(7) Satisfactory elemental or mass spectral analytical data were obtained.

(8) The assignment of the *anti* relationship between the 7-methoxymethyl and carbonyl groups of **2**, which follows clearly from the course expected for the Diels–Alder addition on steric grounds, is supported by the subsequent transformation to prostaglandins E_2 and $F_{2\alpha}$.

(9) J. F. W. McOmie and M. L. Watts, *Chem. Ind.* (London), 1658 (1963).

(10) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(11) For nomenclature with regard to stereochemical orientation, see B. Samuelsson, *Angew. Chem. Intern. Ed. Engl.*, **4**, 410 (1965).

(12) See, for example, E. J. Corey and K. Achiwa, *Tetrahedron Lett.*, 1837 (1969).

(13) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **46**, 2799 (1963).

(14) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(15) The required phosphonium bromide salt was prepared from 5-bromopentanoic acid and triphenylphosphine in acetonitrile at reflux.

(16) Prepared from natural prostaglandin E_2 kindly provided by Professor Bengt Samuelsson.

(17) (a) N. H. Andersen, *J. Lipid Res.*, **10**, 316 (1969); (b) K. Grèen and B. Samuelsson, *ibid.*, **5**, 117 (1964).

with synthetic *dl*-prostaglandin $F_{2\alpha}$ also was chromatographically identical with a sample similarly prepared from the natural hormone.

The stereoselective formation of the *cis*-$\Delta^{5,6}$ olefin is in accord with expectations from previous experience[18] with the dimethyl sulfoxide procedure and also with model experiments involving a number of simple aldehydes and the ylide from 5-triphenylphosphoniopentanoic acid.

Oxidation of **14** by chromic (two-phase) reagent[19] and removal of the tetrahydropyranyl protecting groups using acetic acid–water (2:1) at 37° for 3 hr afforded in 70% yield *dl*-prostaglandin E_2 (**16**) obtained in pure form (as an oil) by chromatography on acid-washed silica gel. The synthetic *dl*-prostaglandin E_2 exhibited the same ir and nmr spectra as the natural hormone and identical chromatographic behavior. The mass spectra and chromatographic behavior of the methyl ester obtained from *dl*-**16** with diazomethane and natural prostaglandin E_2 methyl ester were identical.[20]

Selective reduction of the *cis*-Δ^5 bond of the intermediate bistetrahydropyranyl ether **16** would afford a precursor of prostaglandins E_1 and $F_{1\alpha}$. Although preliminary results (using P-1 nickel boride catalyst[21]) indicate that these monounsaturated prostaglandins can be obtained in this manner, discussion of this aspect of the synthetic work is deferred pending completion of the hydrogenation studies.[22] We also plan to utilize the optically active hydroxy acid derived by hydrolysis of the lactone **3** for the synthesis of natural prostaglandins; preliminary experiments demonstrate that the hydroxy acid is easily resolved.[23]

(18) See E. J. Corey and E. Hamanaka, *J. Amer. Chem. Soc.*, **89**, 2758 (1967), and also E. Hamanaka, Ph.D. Thesis, Harvard University, 1967, for additional examples.

(19) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 143.

(20) Bioassay of the synthetic (racemic) prostaglandins E_2 and $F_{2\alpha}$ by measurement of smooth muscle contraction showed responses at concentrations in the range 10^{-9} to 10^{-8} g/ml, corresponding to a potency one-half that of the natural hormones. We are indebted to Dr. Peter Ramwell and Mr. Reginald Jessup for these biological tests.

(21) C. A. Brown and H. C. Brown, *J. Amer. Chem. Soc.*, **85**, 1003 (1963).

(22) Hydrogenation of prostaglandin $F_{2\alpha}$ to form prostaglandin $F_{1\alpha}$ using a palladium catalyst has been already realized by Professor Bengt Samuelsson [*J. Biol. Chem.*, **239**, 4091 (1964)] and applied to the synthesis of tritium-labeled prostaglandin $F_{1\alpha}$.

(23) This work was supported by the National Institutes of Health.

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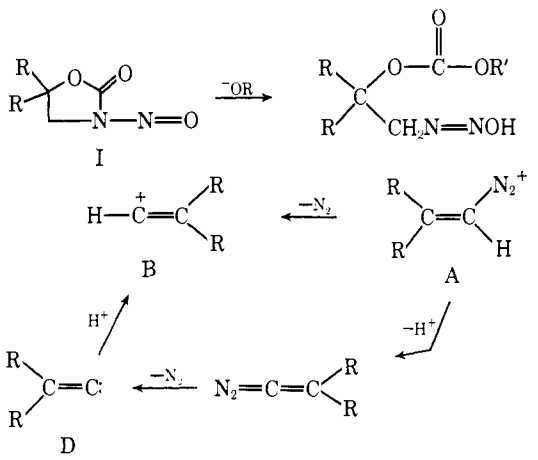
A New Synthesis of Vinyl Halides and Vinylsilanes *via* Alkaline Decomposition of 5,5-Dialkyl-3-nitrosooxazolidones

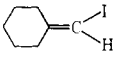
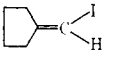
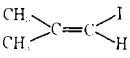
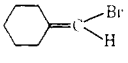
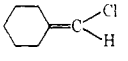
Sir:

Vinyl cations (B) or unsaturated carbenes (D) have been suggested as intermediates in the basic decomposition of 5,5-dialkyl-3-nitrosooxazolidones.[1,2] As it was expected that halide ions would react with B but not D,[3]



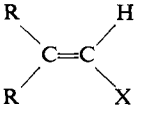
several nitrosooxazolidones were treated with alkoxide in the presence of a large excess of halide ions. The vinyl halides listed in Table I were obtained in high yield.

Table I. Vinyl Halides[a–c]

Compd	Structure	Bp, °C (mm)[d]	Yield, %[e]
IIa		45–47 (0.2)	82
III		83–85 (15)	81
IV		126–127 (753)	80
IIb		78–80 (20)	73
IIc		160–161 (755)	78

[a] Satisfactory elemental analyses were obtained for the new compounds III and IV. [b] The authors are indebted to Professor Dietmar Seyferth for furnishing infrared spectra of authentic IIa–c. [c] Saturated solutions (room temperature) of the alkali metal halides in 2-methoxyethanol employed had the following approximate concentrations: NaI (27.4 g/100 ml), LiBr (22.3 g/100 ml), LiCl (13.3 g/100 ml). [d] Boiling point ranges were determined on a short-path distillation apparatus. Isolated products all were of >96% purity by glpc. Analytical samples were isolated by preparative glpc. [e] Yields (isolated, ±3%) are reported as an average of two or more runs.

Thus a new synthesis of vinyl halides (II–IV) is at hand.



II, R = $-(CH_2)_5-$
a, X = I
b, X = Br
c, X = Cl

III, R = $-(CH_2)_4-$
X = I

IV, R = CH_3
X = I

In a typical reaction (synthesis of IIb), a 20% solution of lithium 2-methoxyethanolate in 2-methoxyethanol was added over a period of about 15 min to a well-stirred solution of 9.2 g (0.05 mol) of nitrosooxazolidone in 120 ml of 2-methoxyethanol saturated with anhydrous lithium bromide at room temperature (22.3 g/100 ml). The temperature was held at or below 40° after the initiation of the vigorous exothermic reaction. The theo-

(1) M. S. Newman and A. Kutner, *J. Amer. Chem. Soc.*, **73**, 4199 (1951).

(2) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969)

(3) Lithium bromide and other strong nucleophiles have been used to trap the 3-phenylcyclopropyl cation generated from N-nitroso-N-2-phenylcyclopropylurea using experimental conditions very similar to those presented herein: W. Kirmse and H. Schütte, *J. Amer. Chem. Soc.*, **89**, 1284 (1967).