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.

J. Alan Webber, Earle M. Van Heyningen, Robert T. Vasileff
The Lilly Research Laboratories, Eli Lilly and Company
Indianapolis, Indiana
Received April 28, 1969

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).

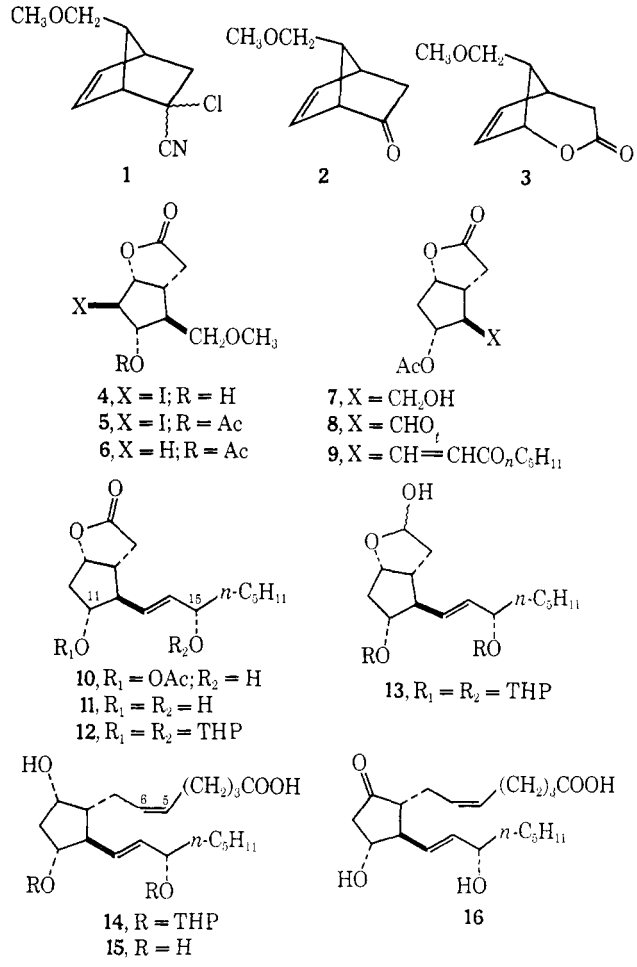
(3) For a review on prostaglandins and the definition of primary prostaglandins, see S. Bergström, *Science*, **157**, 382 (1967).

(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. Gréen 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 $F_{1\alpha}$.

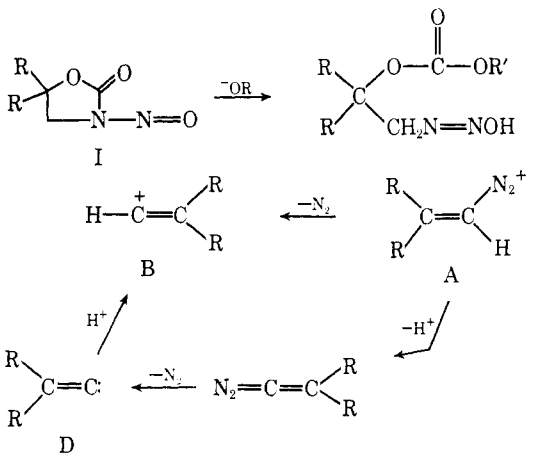
(23) This work was supported by the National Institutes of Health.

E. J. Corey, Ned M. Weinshenker
Thomas K. Schaaf, Willy Huber
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received July 18, 1969

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

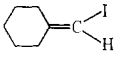
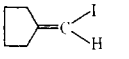
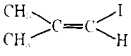
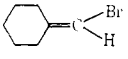
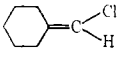
Sir:

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]



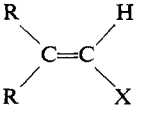
several nitrosooxazolidones were treated with alkoxide in the presence of a large excess of halide ions. The vinyl halides listed in Table I were obtained in high yield.

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).