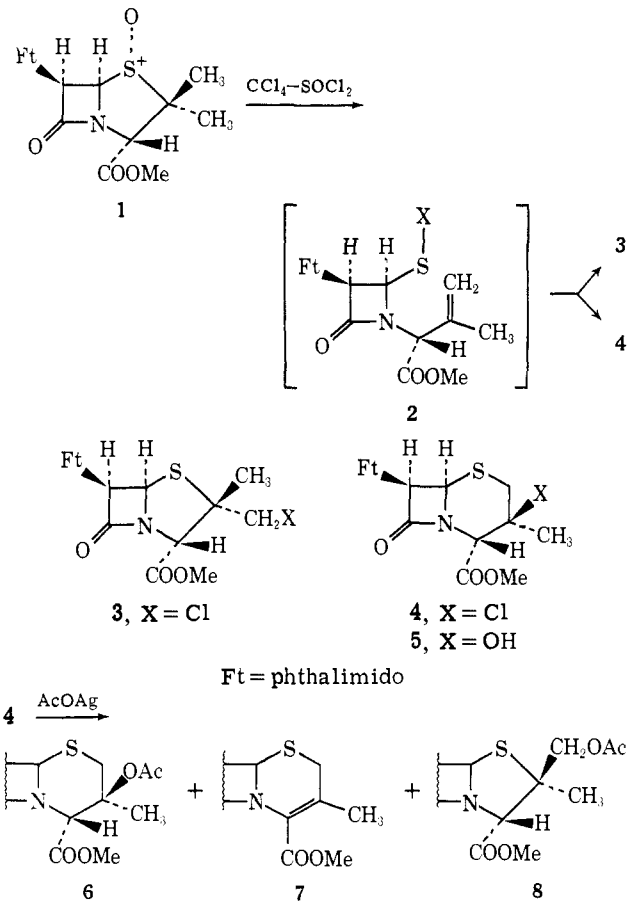
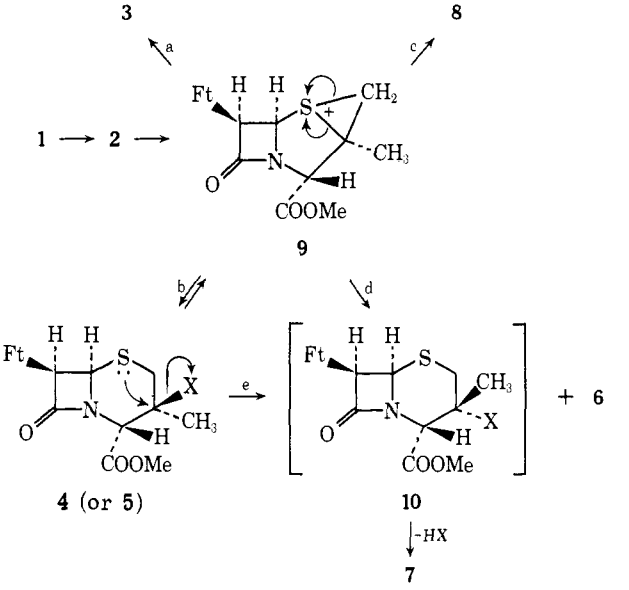
Evidently nucleophilic displacement of the 3-chloro substituent proceeds with both retention and inversion of configuration at C_3 resulting in products **6** and **7** In



addition, the synthesis of **8** from **4** represents the first conversion of a cepham system to a penam system. In order to determine if ring contraction could also be achieved with 3-hydroxycephams, a similar reaction with **5** was investigated. When **5** is heated with thionyl chloride in carbon tetrachloride in the presence of triethylamine, a mixture of **3**, **4**, and **7** in the ratio of *ca.* 1:4:1 is obtained in nearly quantitative yield. The formation of **3** from **5** represents a second example of ring contraction of a cepham to a penam.

Mechanistically the ring contraction of 3-substituted cephams to 2-substituted methylpenicillins is closely related to the ring expansion of penicillin sulfoxides to cephalosporins.[9,13] The intermediacy of **9** has been suggested in the ring expansion reaction,[2-6] and we believe that the ring contraction also occurs *via* **9**. The evidence is presented below in support of the common intermediacy of **9** in both the ring expansion and ring contraction processes.

We propose that the rearrangement of **1** to **3** and **4** *via* **2** (X = OH and Cl) involves initial addition of the sulfenyl chloride grouping to the appropriately positioned olefin to give thiiranium ion **9**.[14] This intermediate in turn undergoes ring opening by nucleophilic attack of chloride ion *via* pathway a and/or b giving **3** and **4**.[15] During ring contraction (**4** → **8** and **5** → **3**) the first step is formation of the carbonium ion which is stabilized by nucleophilic sulfur giving **9**. The episulfonium ion **9** is subsequently opened by anions (pathway a or c) yielding **3** or **8**, as well as the clinal conformer **6** and the periplanar isomer **10** (pathway d).



The latter product is easily transformed to the olefin **7**. An alternate mechanism for the formation of **6** and **10** from **4** can also involve nucleophilic displacement of chloride by acetate (pathway e). Similarly, **4** and **10** (X = Cl) can be formed from **5** by nucleophilic displacement of hydroxyl by chloride.

Acknowledgment. We wish to acknowledge our many helpful discussions with M. Gorman and D. O. Spry of the Lilly Research Laboratories, and Professor E. C. Taylor of Princeton University.

(13) R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, 36, 1259 (1971).

(14) W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, 8, 482 (1969), and references therein.

(15) The formation of **3** and **4** can be explained by assuming an intermediate **9** existing in two configurations. The bridging methylene group can be attached to the sulfur from the α or the β face resulting in α or β episulfonium ions. For a detailed discussion, see: R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Accounts Chem. Res.*, submitted for publication.

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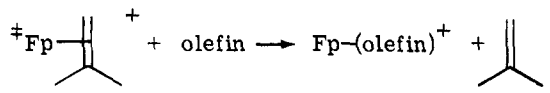
Stereospecific Reduction of Epoxides with Sodium (Cyclopentadienyl)dicarbonylferrate. A New Route to Cationic Iron–Olefin Complexes

Sir:

We recently reported the preparation of cationic iron–olefin complexes of general constitution h^5-$C_5H_5Fe(CO)_2(olefin)^+$ through an exchange reaction employing the readily available isobutylene complex **1**.[1]

We wish now to report an alternative and facile synthesis of these cations employing epoxides as starting materials. The sequence provides a general method for the synthesis of complexes of this type which are

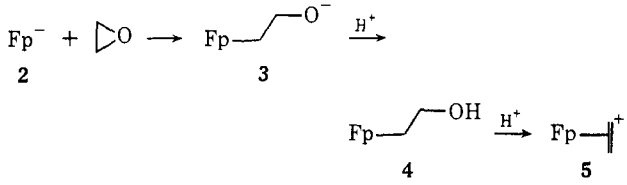
(1) W. P. Giering and M. Rosenblum, *Chem. Commun.*, 441 (1971).



1, $^{\ddagger}Fp \equiv h^5\text{-}C_5H_5Fe(CO)_2$

otherwise not preparable,[2] and at the same time constitutes an effective and simple method for the reduction of epoxides to olefins. Moreover, the reduction occurs stereospecifically with complete retention of configuration and can be effected in the presence of other reducible functions such as aldehyde and ester groups.

Treatment of epoxides at or below room temperature with tetrahydrofuran solutions of sodium (cyclopentadienyl)dicarbonylferrate (**2**)[6] results in their rapid conversion to the alkoxides **3**.[7] These, on reaction *in situ* with 2 equiv of fluoroboric or hexafluorophosphoric acid, are converted instantaneously and in high overall yield to the olefin complex **5**, which may be precipitated from solution by the addition of ether. The olefin salts are in turn readily decomposed at room temperature by brief treatment with sodium iodide in acetone, liberating the olefin.



The simplicity and convenience of the method are illustrated by the following procedure for the reduction of glycidaldehyde. A solution of 0.37 g (5 mmol) of glycidaldehyde in 10 ml of THF was added dropwise at 0° in a nitrogen atmosphere to a solution of the anion **2**, prepared from 0.88 g (2.5 mmol) of cyclopentadienyliron dicarbonyl dimer in 10 ml of THF. After 30 min at room temperature, the solution was cooled to 0°, 1.8 ml of fluoroboric acid (48%) was added dropwise, and the product was precipitated by the addition of ether. This was collected and recrystallized once from acetone–ether to give 1.50 g (94%) of pure salt. Decomposition was effected by treating an acetone solution of the salt with 1 equiv of sodium iodide for 15 min at room temperature. At the end of this period an nmr spectrum showed only the presence of acrolein (100%, benzene as internal standard) and cyclopentadienyliron dicarbonyl iodide.

(2) Previous methods employed for the synthesis of these and related cationic transition metal–olefin complexes involved protonation of h^1-allyl complexes,[3] hydride abstraction from an alkyl–metal complex,[4] or treatment of the complex metal halide with Lewis acids in the presence of an olefin.[5]

(3) M. L. H. Green and P. L. I. Nagy, *J. Chem. Soc.*, 189 (1963).

(4) (a) M. L. H. Green and P. L. I. Nagy, *J. Organometal. Chem.*, **1**, 58 (1963); (b) D. J. Ehntholt, G. F. Emerson, and R. C. Kerber, *J. Amer. Chem. Soc.*, **91**, 7547 (1969).

(5) E. O. Fischer and K. Fichtel, *Chem. Ber.*, **94**, 1200 (1961); **95**, 2063 (1962).

(6) Readily prepared by reduction of $[h^5\text{-}C_5H_5Fe(CO)_2]_2$ with sodium amalgam: E. O. Fischer and R. Böttcher, *Z. Naturforsch.*, **106**, 600 (1955).

(7) The reactions of other complex transition metal anions with epoxides have also been reported to yield analogous hydroxyethyl complexes: R. F. Heck and D. S. Breslow, *J. Amer. Chem. Soc.*, **83**, 4023 (1961); R. S. Heck, *ibid.*, **85**, 1460 (1963); G. N. Schrauzer and R. J. Windgassen, *ibid.*, **89**, 143 (1967); Y. Takegami, Y. Watanabe, T. Mitsudo, and H. Masada, *Bull. Chem. Soc. Jap.*, **42**, 202 (1969); F. R. Jensen, V. Madan, and D. H. Buchanan, *J. Amer. Chem. Soc.*, **92**, 1414 (1970).

Those epoxides which have been converted to their corresponding olefin complex and thence to the free olefin with sodium iodide are summarized in Table I.

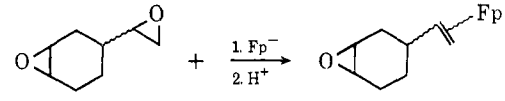
Table I. Conversion of Epoxides to Olefin–Iron Complexes

Epoxides	Yield of Fp-(olefin)$^+$ complex, %	Ref
Ethylene oxide	90	3, 4a, 5
Propylene oxide	91	3, 4a, 5
1-Butene oxide	91	3
cis-2-Butene oxide	64	5
trans-2-Butene oxide	50	This paper[a]
Styrene oxide	62	4b
trans-Stilbene oxide	83	This paper[a]
cis-Stilbene oxide	82	This paper[a]
Cyclohexene oxide	66	5
Butadiene monooxide	91	5
Acrolein oxide	90	This paper[a]
trans-Ethyl crotonate oxide	96	This paper[a]
4-Vinylcyclohexene dioxide (**6**)	50 (**7**)	This paper[a]

[a] All new cations were characterized as their BF_4^- or PF_6^- salts by elemental analysis and by their ir and nmr spectra.

For all these complexes the yield of olefin, determined by decomposition of the salt in deuterioacetone and examination of the nmr spectrum of the resulting solution in the presence of an internal standard, was quantitative.

The relative rates of reaction of the anion **2** with terminal and internal epoxides reflect the large steric demand of this reagent. Thus, while the reaction of **2** with terminal epoxides is essentially complete at room temperature within several minutes, several hours are required for complete consumption of *cis*- or *trans*-stilbene, cyclohexene, and *cis*- and *trans*-2-butene epoxides. Neither cyclooctene nor *exo*-norbornene epoxide was observed to react on prolonged exposure to the anion at room temperature. Some advantage may be taken of these rate differences as illustrated by the selective conversion of 4-vinylcyclohexene diepoxide (**6**) to a mixture of stereoisomeric monoepoxide–olefin complexes **7**.



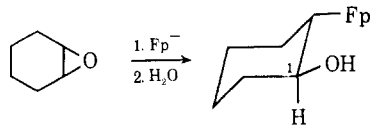
Neither carbonyl nor ester functions appear to interfere with the reaction sequence since both acrolein and *trans*-ethyl crotonate epoxides may be converted in high yield to their corresponding cationic olefin complexes from which the free olefin may in turn be liberated.

The transformation of epoxide to olefin complex proceeds with retention of configuration, as is indicated by the conversion of *cis*- and *trans*-2-butene, *cis*- and *trans*-stilbene, and *trans*-ethyl crotonate epoxides to the stereochemically unchanged olefin complexes (>98% retention). Thus, vpc analysis of the products derived from the sodium iodide decomposition of the *cis*- and the *trans*-2-butene complexes failed to detect any of the isomeric olefin. Similarly, decomposition

of solutions of either the *cis*- or *trans*-stilbene complex[8] alone or in the presence of iodide gave only the corresponding olefin, while similar decomposition of the *trans*-crotonate complex gave only ethyl *trans*-crotonate, as determined by nmr spectra of the reaction solutions. The sequence therefore provides a synthetically useful complement to the reduction of epoxides through conversion to phosphorus betaines with triphenylphosphine[9] or lithium diphenylphosphide,[10] which results in stereochemical inversion. It constitutes a convenient alternative to the reduction of epoxides by conversion to iodohydrins and reduction of these with zinc or stannous chloride.[11]

The stereochemical result may be readily accounted for by a mechanism involving initial SN2 opening of the epoxide by the complex anion, followed by a trans migration of the organometallic group concerted with the loss of water from the oxonium ion formed on protonation of the alcohol.[12]

The intermediate alcohols may be isolated as labile, air-sensitive yellow solids, by quenching solutions of the alkoxide **3** with water. The nmr spectrum of the alcohol derived from cyclohexene oxide exhibits a broad multiplet (19 Hz at half-height) at τ 6.90 for the proton at C_1, consistent with an axial conformation for this proton resulting from trans opening of the epoxide ring.[13,14]



While the intermediate alcohols are generally unstable, the related alkoxides, which may be precipitated from the initial reaction solution by the addition of ether, are relatively stable. This is most strikingly illustrated by the alcohol derived from *trans*-stilbene oxide which is exceedingly labile in solution and in the solid state. By contrast the corresponding alkoxide is a stable yellow solid which can be stored for prolonged periods of time without apparent decomposition.

The further use of these substances and of the cationic metal–olefin complexes will be reported shortly.

Acknowledgment. This work was supported by grants from the National Science Foundation (GP-27991-X) and by the National Institutes of Health (GM-16395) which are gratefully acknowledged.

(8) The *trans*-stilbene salt decomposes rapidly in nitromethane solutions above 0° to give the nitromethane-complexed cation, $[C_5H_5Fe(CO)_2CH_3NO_2]^+$, as a crystalline orange salt: ir (KBr) 2030, 2080 (C≡O) 1540, 1340 cm^{-1} (NO_2); nmr (CD_3NO_2) τ 4.50 (s, 5, Cp), 5.64 (s, 3, CH_3).

(9) G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).

(10) E. Vedejs and P. L. Fuchs, *J. Amer. Chem. Soc.*, **93**, 4070 (1971).

(11) J. W. Cornforth, R. H. Cornforth, and K. K. Mathews, *J. Chem. Soc.*, 112 (1959).

(12) The stereochemical constraints involved in participation of the complex organometallic substituent in elimination reactions have been examined in a previous report: A. Cutler, R. W. Fish, W. P. Giering, and M. Rosenblum, *J. Amer. Chem. Soc.*, **94**, 4354 (1972).

(13) Alone among these alcohols, that derived from *trans*-ethyl crotonate is a stable yellow-orange crystalline material, mp 64–64.5°. Its nmr spectrum (CD_3NO_2), τ 6.07 (q + m, 3, CH_2 + β-H), 6.75 (d, 1, J = 6 Hz, OH), 7.67 (d, 1, J = 6 Hz, α-H) 8.73 (t, 3, J = 7 Hz, CH_3CH_2), 8.79 (d, 3, J = 6 Hz, CH_3CHOH), indicates that epoxide ring opening has taken place through displacement at the α carbon atom of the ester. It seems likely that it is the electron-withdrawing ester function which is largely responsible for stabilizing the metal–carbon σ bond in this substance.

(14) J. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 288. Jensen, Madann, and Buchanan[7] have recently reported similar results in the reaction of cyclohexene oxide with pyridine[bis-(dimethylglyoximato)]cobalt(I), and have confirmed this assignment through an examination of the spectra of the two epimeric alcohols.

(15) Gillette Fellow, 1970–1972.

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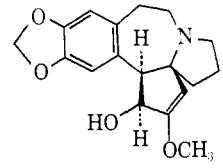
Received May 12, 1972

The Total Synthesis of Cephalotaxine

Sir:

Cephalotaxine is the parent member of the Cephalotaxus group of alkaloids, several of which have shown significant inhibitory activity against experimental lymphoid leukemia. Structural elucidation by a combination of chemical and X-ray crystallographic studies has shown cephalotaxine to have the unique structure and stereochemistry indicated in formula **1**.[1–4] In this



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paper we wish to report the first total synthesis of racemic cephalotaxine.

Condensation of prolinol[5] with 3,4-methylenedioxyphenylacetyl chloride[6] in acetonitrile solution at −20° in the presence of suspended potassium carbonate gave the alcohol **2** as a viscous oil (82% yield). Oxidation of **2** with dicyclohexylcarbodiimide, dichloroacetic acid, and dimethyl sulfoxide[7] gave the oily aldehyde **3**, isolated by chromatography in 70% yield [nmr peaks ($CDCl_3$) at δ 9.50 (1 H, d, J = 1.5 Hz); ir max (film) 1720 cm^{-1}]. Cyclization of aldehyde **3** to tetracyclic enamide **4**, mp 122–123°, was accomplished in 85% yield by stirring at room temperature in chloroform solution in the presence of boron trifluoride etherate [nmr peaks ($CDCl_3$) at δ 6.65 (1 H, s), 6.52 (1 H, s), 5.96 (1 H, s, vinyl), 5.90 (2 H, s), 3.68 (2 H, t, J = 3 Hz), 3.26 (2 H, s), 2.74 (2 H, t, J = 3 Hz), 1.90 (2 H, m); ir max ($CHCl_3$) 1650 cm^{-1}]. Enamide **4** upon reduction with lithium aluminum hydride in refluxing tetrahydrofuran gave enamine **5** (100%), mp 82–83° [nmr peak (C_6D_6) at δ 5.00 (1 H, s)].

Treatment of enamine **5** with 2-acetoxypropionyl chloride[8] in refluxing acetonitrile in the presence of

(1) W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963).

(2) (a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969); (b) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. Rohwedder, *ibid.*, 815 (1970); (c) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972); (d) R. E. Perdue, Jr., L. A. Spetzman, and R. G. Powell, *Amer. Hort. Mag.*, **49**, 19 (1970).

(3) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969).

(4) For speculative proposals concerning the biogenetic origin of these alkaloids, see: (a) V. A. Snieckus in "The Alkaloids," Vol. 1, The Chemical Society Specialist Reports, 1971, p 149; (b) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972).

(5) O. Vogl and M. Pohm, *Monatsh. Chem.*, **83**, 541 (1952).

(6) E. R. Shepard, H. D. Porter, J. F. Noth, and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).

(7) J. G. Moffatt in "Oxidation," Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N. Y., Chapter 1.

(8) E. B. Reid and G. Denny, Jr., *J. Amer. Chem. Soc.*, 81, 4632 (1959).