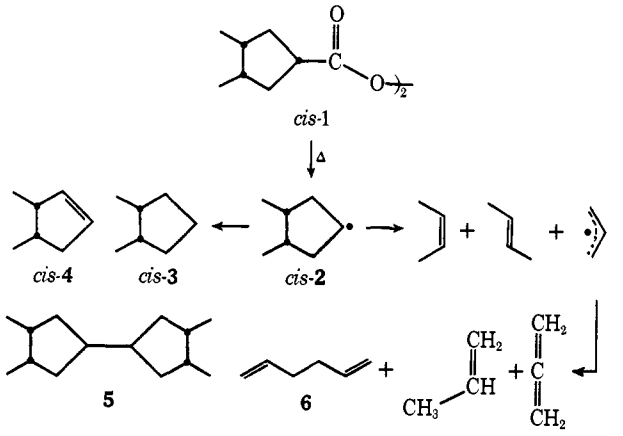
Table I. Pyrolyses of *cis*- and *trans*-Bis(3,4-dimethylcyclopentyl)formyl Peroxides (*cis*- and *trans*-**1**)[a,b]

Peroxide	Pyrol temp, °C	Chromosorb P, g	CO_2[c]		CH_2=C=CH_2				*trans*-**3**	*trans*-**4**	*cis*-**3**	*cis*-**4**			**5**[d]
trans-**1**[e] (0.005)	505	10	73.6	3.8	3.6	12.1	5.4	5.2	11.0	16.3	0.4	0.5		5.5	21.4
cis-**1**[f] (0.005)	505	10	70.5	3.7	3.6	10.7	4.7	2.8	0.6	0.9	6.6	10.3	5.3		21.8
cis-**1**[f] (0.010)	505	5	86.1	3.1	1.8	4.3	2.3	1.0	0.2	0.3	3.7	5.6	6.9		59.3
cis-**1**[f] (0.005)	602	10	95.3	12.9	11.7	7.1	4.2	0.7	0.7	1.2	12.4	13.6	1.1		5.6

[a] Less than 5% of volatile products are unaccounted for by glpc analysis for 505° reactions, and less than 14% for the 602°. [b] All starting materials and products were completely characterized spectroscopically and through elemental analyses, and most products were compared with authentic samples. [c] Analyzed using Ascarite as an absorbant. [d] The stereochemistry of **5** is still ambiguous. [e] 98% pure trans (2% cis). [f] 94.5% pure cis isomer (5.5% trans).

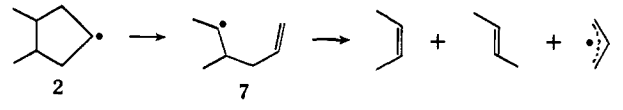
stable under the reaction conditions at 505°, but isomerize substantially at 602°.[8]

Scheme I



The conclusion that one seems compelled to reach from the data in Table I is that a partially cleaved intermediate, such as **7**, must intercede in this reaction at least to a significant extent, as depicted in Scheme II.[10] Under conditions (505°) where *no* isomerization

Scheme II



of the 2-butenes is found to occur, one obtains near *identical* ratios of *cis*- and *trans*-2-butenes from cleavage of the *cis*- or *trans*-3,4-dimethylcyclopentyl radicals. The fact that disproportionation products **3** and **4** in each case show only minimal loss of stereochemistry refutes the possibility of substantial reversibility of the initial single-bond cleavage. Thus the possibility of concurrent, but independent, geometrical isomerization and concerted cleavage seems unambiguously ruled out.

It thus appears that Longuet-Higgins' conclusion that radical electrocyclic processes should not be concerted has been borne out by experiment. It remains to be demonstrated whether differences in stereospecificity can be detected for more, or less, "allowed" radical processes. A point of interest in this regard is our very preliminary observation that the 4-cycloheptenyl radical, generated analogously, cleaves to butadiene in 13% yield at temperatures >650°. Indications are that this reaction is not nearly so clean as that of **1**. Additional results relating to these studies and related ones will be reported in the future.

(8) This is rather curious since the geometrical isomerizations of the 2-butenes have an activation energy of >60 kcal/mol.[9]

(9) (a) B. S. Rabinovitch and K. W. Michel, *J. Amer. Chem. Soc.*, **81**, 5065 (1959); (b) R. B. Kundall and T. F. Palmer, *Trans. Faraday Soc.*, **57**, 1936 (1961).

(10) No disproportionation products from **7** have yet been distinguished, although they might be present as minor constituents.

(11) Fellow of the Alfred P. Sloan Foundation, 1970–1972.

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Total Synthesis of Prostaglandins. II. Prostaglandin E_1

Sir:

Several elegant total synthetic routes leading to prostaglandin E_1 (PGE_1) have already appeared.[1] We herein report a short novel total synthesis of PGE_1 in in its naturally occurring form. The topologically obvious dissection of the prostanoic acid skeleton into C_7 and C_8 side chains and a cyclopentane ring is the structural basis for our approach to the synthesis of prostaglandins. Recently we described our procedure for uniting the side chains and ring in a five-step synthesis of *dl*-15-deoxyprostaglandin E_1 from cyclopentadiene.[2] As an extension of this study, we have now completed the synthesis of PGE_1 (V).

The following series of reactions was used for the preparation of 3(*S*)-(α-ethoxy)ethoxy-1-lithio-1-*trans*-octene (I). The hydroalumination method of Zweifel and Whitney[3] was used to convert 3(*S*)-1-octynol,[4]

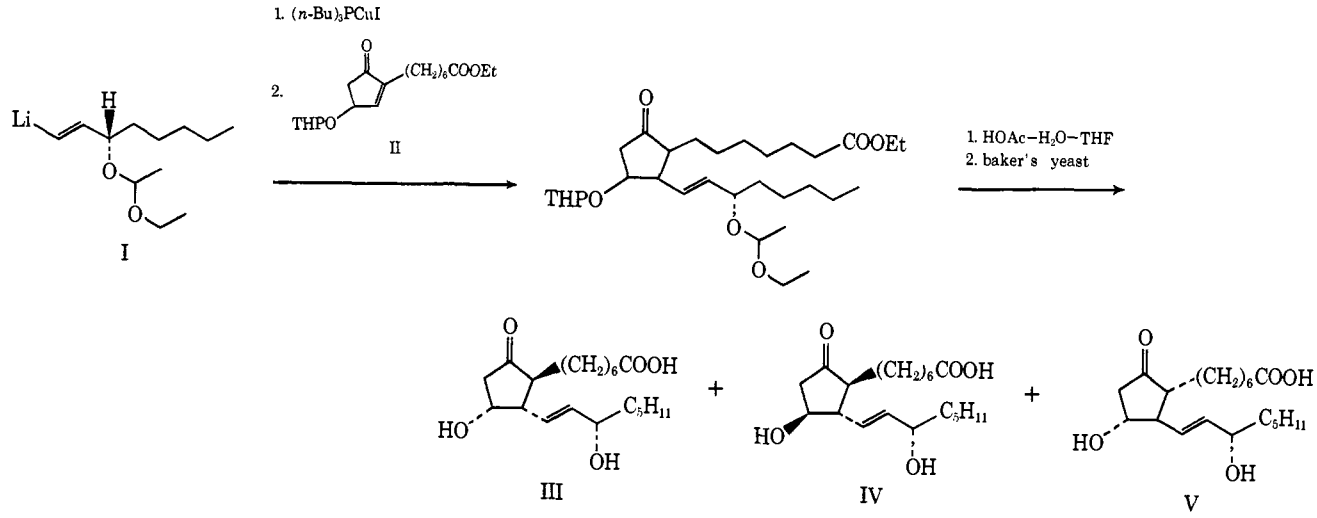
(1) (a) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, **90**, 3245 (1968); (b) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968); (c) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *ibid.*, **91**, 19 (1969); (d) E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970); and (e) D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, Z. S. Zelawski, and N. L. Wendler, *Chem. Commun.*, 1258 (1970).

(2) Paper I in this series: C. J. Sih, R. G. Salomon, P. Price, G. Peruzzotti, and R. Sood, *J. Chem. Soc., Chem. Commun.*, 240 (1972).

(3) G. Zweifel and C. C. Whitney, *J. Amer. Chem. Soc.*, **89**, 2753 (1967).

(4) J. Fried, C. Lin, M. Mehra, W. Kao, and P. Dalven, *Ann. N. Y. Acad. Sci.*, **180**, 38 (1971).

Scheme I



$[\alpha]^{23}D$ −22.3° (*c* 10 in ether) (reported values: $[\alpha]D$ −19.8°[4] and $[\alpha]D$ −21°[5]), into 3(*S*)-hydroxy-1-iodo-1-*trans*-octene, which was in turn transformed into 3(*S*)-(α-ethoxy)ethoxy-1-iodo-1-*trans*-octene by reaction with ethyl vinyl ether in the presence of an acid catalyst. Treatment of the latter compound with lithium metal gave I in an overall yield of about 25%. The procedure for the preparation of 2-(6′-carboethoxyhexyl)-2-cyclopentene-4-tetrahydropyranoxy-1-one (II) was previously described.[2]

The prostanoic acid skeleton was constructed by condensing II (500 mg) with 2 molar equiv of I, in presence of 1 molar equiv of tri-*n*-butylphosphine–copper(I) iodide complex[6] at 0° in ether. After cleaving the protecting groups by acid treatment[7] and the ester grouping with baker's yeast,[8] the mixture was chromatographed over a silicic acid–Celite column. Two major diastereomeric products[9] were obtained by elution of the column with a gradient system comprised of benzene–ethyl acetate. The first product (113 mg) was obtained as an oil, whose physical constants[10] were in good agreement with 15-epi-*ent*-PGE_1 (IV). Its circular dichroism (CD) spectrum exhibited a positive Cotton effect ($[\theta] \times 10^{-3} = +12.05°$ at λ 296 nm), whereas its acid dehydration product, 15-epi-*ent*-PGA_1, λ_{max}^{alc} 217 nm (ε 11,000), afforded a negative Cotton effect ($[\theta] \times 10^{-3} = -50.4°$ at 231 nm), in contradistinction to the CD curves[11] of natural PGE_1 and PGA_1, respectively. The second product (107 mg), mp 115–116° $[\alpha]^{20}D$ −54.3° (*c* 1.0, THF),[12] $[\alpha]^{20}D$ −65.1° (*c* 0.43, ethanol), was found to be identical (infrared, nuclear magnetic resonance, and mass spectra) with an authentic specimen of natural PGE_1, prepared by biosynthesis.[13] Aside from these major products, a small quantity of 11,15-epi-*ent*-PGE_1 (III)[14] (26 mg) was also formed in the reaction (Scheme I). However, no apparent 8-iso-PGE_1 and 11-epi-PGE_1 were detectable.[15] This product profile reveals that this method possesses considerable stereoselectivity in that the 1,4 addition by the vinyl copper reagent appears to proceed almost exclusively from the least hindered side of II and that the relative stereochemistry of the substituents at C-8, C-12, and C-11 is all trans.[16]

Acknowledgment. The authors are indebted to Professor Josef Fried for a sample of the (−)-α-phenylethylamine salt of 3(*S*)-octynol phthalic ester and to Dr. John Pike for samples of 11-epi-, 15-epi-, and 8-isoprostaglandins.

(5) R. Pappo, P. Collins, and C. Jung, *Ann. N. Y. Acad. Sci.*, **180**, 64 (1971).

(6) G. B. Kaufman and L. A. Teter, *Inorg. Syn.*, 7, 9 (1963).

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

(8) The prostanoic acid esters were exposed to 15 g of dried yeast (Red Star) in 500 ml of 0.1 *M* phosphate buffer, pH 7.0, for 16 hr at 25° on a rotary shaker.

(9) The concept of utilizing the optically active hydroxylated 8-carbon side chain for the resolution was first employed by J. Fried, *et al.*, *J. Amer. Chem. Soc.*, **93**, 5594 (1971).

(10) The chromatographic behavior and infrared, nuclear magnetic resonance, and mass spectra of this substance were identical with those of an authentic sample of 15-epi-PGE_1, provided to us by John Pike.

(11) O. Korver, *Recl. Trav. Chim. Pays-Bas Belg.*, **88**, 1070 (1969).

(12) Under the same conditions, our sample of natural PGE_1 (mp 115–116°) afforded values of $[\alpha]^{20}D$ −55.2° (*c* 1.6, THF) and −66.1° (*c*, 0.57, ethanol). This differs somewhat from the reported value, $[\alpha]^{25}D$ −58.3° (*c* 0.47, THF): E. J. Corey and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 7319 (1971).

(13) C. Takeguchi, E. Kohno, and C. J. Sih, *Biochemistry*, **10**, 2372 (1971).

(14) The infrared, nuclear magnetic resonance, and mass spectra of this substance and its chromatographic behavior were identical with those of an authentic sample of 11,15-epi-PGE_1.

(15) PGE_1, 8-iso-PGE_1, and 11-epi-PGE_1 can be separated on thin layer plates by two developments in the solvent system, $CHCl_3$–EtOH–HoAC (90:4:6).

(16) This investigation was supported in part by research grants from the Wisconsin Alumni Research Foundation and the National Institutes of Health (AM-4874 and AM-9688).

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Proton Magnetic Resonance Line Broadening Produced by Association with a Nitroxide Radical in Studies of Amide and Peptide Conformation[1]

Sir:

Morishima, Endo, and Yonezawa[2] have reported contact shifts produced by hydrogen bonding between di-*tert*-butyl nitroxide and several simple organic mole-

(1) This work was supported by a grant from the U. S. Public Health Service, GM 14069, and by a Public Health Service Research Career Development Award, GM 47357, both from the Institute of General Medical Sciences.

(2) I. Morishima, K. Endo, and T. Yonezawa, *J. Amer. Chem. Soc.*, **93**, 2048 (1971).