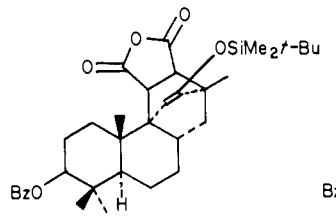
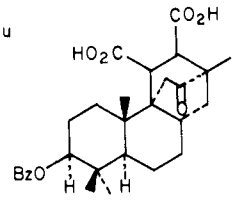
the benzyl ether (**6b**) of ketone **6a** was transformed quantitatively into the corresponding silyl enol ether, reaction of which (unpurified) with maleic anhydride (3.6 equiv in $C_6H_5CH_3$ at 90 °C), involving approach from the *overall* less hindered β face, produced pentacycle **7**. Since the adduct was unstable, it was hydrolyzed



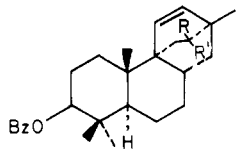
7



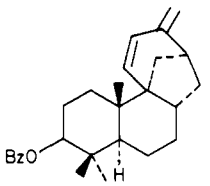
8

(3:2 5% aqueous KOH–$(CH_3)_2CO$ at reflux) (84% from **6b**) to the keto acid **8**,[11] which in the crude, amorphous state was oxidatively decarboxylated with $Pb(OAc)_4$ in O_2-saturated pyridine at 90 °C, giving (21% after SiO_2 chromatography) the unsaturated ketone **9a**[12] (mp 134–136 °C; ether–hexane).

Reduction of **9a** with $NaBH_4$ (10 equiv in C_2H_5OH at 25 °C) produced (85%) in a 70:30 ratio (by HPLC) the two alcohols **9b** and **9c**. Tosylation of **9b** (excess TsCl in pyridine at 40 °C)



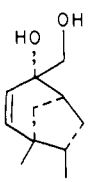
9a, R = R' = O
b, R = OH; R' = H
c, R = H; R' = OH



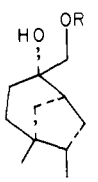
10

induced a [2.2.2] → [3.2.1] skeletal rearrangement, similar to that in the presumed biosynthesis of the stemodane system, with formation (77%) of the conjugated diene **10**.[13]

Oxidation of **10** with OsO_4 in $(C_2H_5)_2O$ and 2 equiv of pyridine (−10 °C → room temperature) proceeded regio- and stereoselectively generating glycol **11**, which was directly hydrogenated (freshly prepared Pt-black in C_2H_5OH at room temperature and 1 atm) to the saturated tetracycle **12a** (after HPLC, mp 173–176 °C; 41% overall from **10**). Exposure of the latter of TsCl



11



12a, R = H
b, R = $SO_2C_6H_4$-*p*-CH_3

(pyridine at 25 °C) yielded monotosylate **12b** (81%) which was transformed to (±)-maritimol benzyl ether through the agency of $LiHB(C_2H_5)_3$ (100 equiv in THF at 25 °C, followed by $NaOH–H_2O_2$ workup). Debenzylation was effected by Li in NH_3 at reflux, giving (±)-maritimol (after HPLC, 60% from **12b**) (mp 212.5–214 °C; ether–hexane) indistinguishable from the natural product on the basis of chromatographic as well as NMR, IR, and MS spectral comparisons.

Acknowledgment. We thank the National Science Foundation for grant support (CHE-77-02023 and CHE 80-02661), the Upjohn Company for fellowship support (J.G.C.), and Dean Norman Doorenbos, University of Southern Illinois, for provision of a maritimol sample. We are also grateful to the National Science Foundation for NMR facilities (GP 28142 and CH 77-08810).

A Short, Economical, and Stereoselective Route to Prostaglandins by Vicinal Alkylation of Cyclopentadiene

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Received April 9, 1981

An unusual number of elegant and ingenious routes to prostaglandins have been explored with success.[1] Recently we have initiated studies of a general approach to this important class of hormones which possess a common structural feature, namely, two vicinal carbon chains attached to a functionalized cyclopentane ring. Our approach has capitalized on the possibility of adding regio- and stereoselectivity two carbon chains on a suitably substituted cyclopentane ring. The methodology[2] involves the formation of a cyclobutanone by cycloaddition of a ketone-bearing anion-stabilizing group to a derivative of cyclopentene or cyclopentadiene followed by regiospecific cleavage of the strained ring with carbon nucleophiles. An alternative strategy[3] is based on the conjugate addition of a cuprate reagent to a cyclopentenone followed by trapping of the intermediate enolate with electrophiles.

The present communication outlines an application of this general methodology to an exceptionally short and economical synthesis of advanced intermediates which can be easily converted into primary prostaglandins and their analogues. *In the present approach, a new reagent, (carbomethoxy)chloroketene* (**1a**), *is used for the stereoselective introduction of both side chains and functionality on cyclopentadiene.*

(Carbomethoxy)chloroketene (**1a**) was generated in situ at room temperature by dropwise addition (7 h) of triethylamine (0.032 mol) in dry hexane (420 mL) to a solution of acid chloride[4] **2a** (0.032 mol) in hexane (120 mL) containing cyclopentadiene (0.2 mol) (Scheme I). Workup and distillation yielded pure **3a** (70%, mp 68 °C).[5] The activating effect of a chlorine substituent on

(11) IR (KBr) 2955, 1731, 1698, 1179; 100 MHz NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.85 (3 H, s), 0.96 (3 H, s), 1.05 (3 H, s), 1.20 (3 H, s), 2.40–3.45 (4 H, m), 4.40 and 4.63 (2 H, AB, J = 12 Hz), 7.33 (5 H, brs).

(12) IR 2916, 1718, 1241, 1221, 729, 678 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 0.88 (3 H, s), 0.99 (3 H, s), 1.10 (3 H, s), 1.15 (3 H, s), 2.03 and 2.50 (2 H, AB, J = 18 Hz), 2.80-3.00 (1 H, m), 4.43 and 4.70 (2 H, AB, J = 12 Hz), 5.83 (1 H, d, J = 8 Hz), 6.43 (1 H, d, J = 8 Hz), 7.32(5 H, brs).

(13) UV λ_{max} (EtOH) 236 nm; 100-MHz NMR ($CDCl_3$) δ 0.93 (3 H, s), 1.02 (3 H, s), 1.15 (3 H, s), 1.95–2.20 (2 H, m), 2.75–3.00 (2 H, m), 3.30–3.55 (2 H, m), 4.41 and 4.67 (2 H, AB, J = 12 Hz), 4.44 (1 H, Brs), 4.58 (1 H, t, J = 1.5 Hz), 5.93 (1 H, dd, J = 10 Hz, 1.5 Hz), 6.08 (1 H, d, J = 10 Hz), 7.31 (5 H, brs).

(1) Recent reviews: (a) Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977. (b) Mitra, A. "Synthesis of Prostaglandins"; Wiley-Interscience: New York, 1977. (c) *Org. Chem. (N.Y.)* **1977**, *36*, 121. (d) Szántay, C.; Novak, L. "Synthesis of Prostaglandins"; Akadémiai Kiadó: Budapest, 1978. (e) Caton, M. P. L. *Tetrahedron* **1979**, *35*, 2705. (f) Newton, R. F.; Roberts, S. M. *Ibid.* **1980**, *36*, 2163.

(2) (a) Cossement, E.; Binamé, R.; Ghosez, L. *Tetraheron Lett.* **1974**, 997. (b) Ghosez, L. *Int. Congr. Ser.*—Excerpta *Med.* **1979**, *No.* **457**, 93. (c) Michel, Ph.; O'Donnell, M.; Binamé, R.; Ghosez, L.; Declercq, J. P.; Germain, G.; Arte, E.; Van Meerssche, M. *Tetrahedron Lett.* **1980**, 2577.

(3) (a) Stork, G.; Isabe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260. (b) Patterson, J. W.; Fried J. H. *J. Org. Chem.* **1974**, 39, 2506. (c) Posner, E. H.; Sterling, S. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*; *Tetrahedron Lett.* **1974**, 2591. (d) Schwarts, J.; Loots, M. J.; Kosugi, M. *J. Am. Chem. Soc.* **1980**, *102*, 1333.

(4) The acid chloride **2a** could be readily prepared by chlorination of monomethyl malonate with SO_2Cl_2 in ether and subsequent reaction with PCl_5. The crude acid chloride contained 10% of dichlorinated material but was used without further purification.

(5) All new compounds gave correct elemental analysis and satisfactory spectral data.

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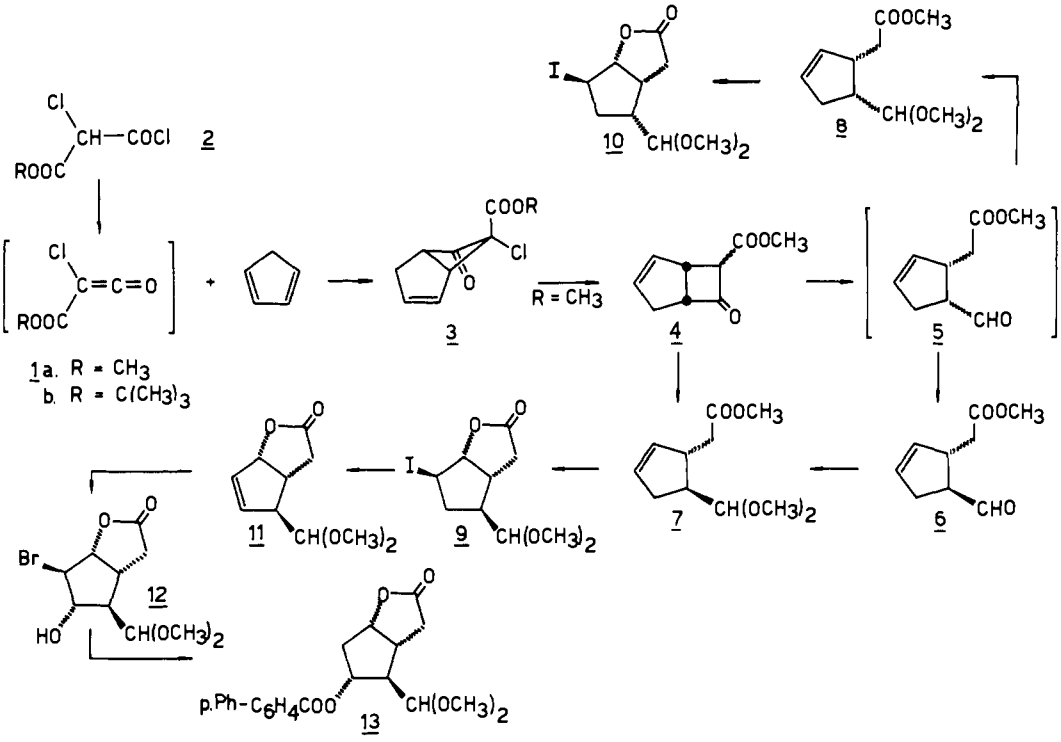
Scheme I



ketenes is again[6] demonstrated since the parent (carbomethoxy)ketene did not cycloadd to cyclopentadiene.

The cycloaddition proceeded with high stereoselectivity as shown by the presence of a single signal for each type of carbon in the ^{13}C NMR spectrum of **3a** and one singlet for the methyl hydrogens of the ester group. However, no secure stereochemical assignment could be made on the basis of these data. An X-ray crystallographic study[7] provided us with an unexpected answer: the ester group of **3a** was in the exo, pseudoaxial configuration. This result contrasted with all previous observations[8] on cycloadditions of ketenes to cyclopentadiene which had been shown to give predominantly the adduct with the larger substituent in the endo, pseudoequatorial configuration. This is indeed the expected consequence of a skew approach of the reactants with minimal steric repulsion.[8] However, in the transition state leading to **3a**, steric repulsions could be largely compensated by a stabilizing interaction between the electron-enriched ester group and the electron-deficient end of the reacting carbon–carbon double bond. Increasing the size of the ester group did not cause any change in this unusual stereochemistry: **3b** was the sole adduct in the reaction of cyclopentadiene with **1b**.

Dechlorination of **3a** with tri-*n*-butyltin hydride (1.3 equiv, AIBN, benzene, reflux) yielded **4** as a mixture of isomers [bp 70 °C (0.05 torr), bulb to bulb, 70%]. Reduction of **4** with $NaBH_4$ (1.5 equiv, CH_3OH, −70 °C) followed by treatment with *1 equiv of sodium methoxide* overnight at room temperature and neutralization with aqueous HCl effected (a) the reduction of the ketone group, (b) the cleavage of the four-membered ring to give the *cis*-aldehyde **5**, (c) the epimerization of **5** to the more stable *trans*-aldehyde **6**: 64%; IR ($CHCl_3$) 1730 cm^{-1} (br); NMR ($CDCl_3$, 200 MHz) δ 9.7 (d, J = 2.02 Hz, 1 H), 5.67 (m, 1 H), 3.68 (s, 3 H), 3.42 (m, 1 H), 2.9–2.25 (m, 5 H). The *trans*-dimethyl acetal **7** could be conveniently obtained by acidification with dry HCl of the crude epimerized aldehyde **6** and reaction with trimethyl orthoformate [1.5 equiv, 20 °C, 24 h, 60% from **4**, bp 80 °C (0.01 torr)]. The stereochemical assignment was secured as follows: reduction of **4** as above followed by treatment with *catalytic amounts of sodium methoxide* for 2 h at room temperature followed by direct acetalization with trimethyl orthoformate gave the *cis*-acetal **8** [73% from **4**, bp 115 °C (0.01 torr)]. Acid hydrolysis (0.1 N HCl) of **8** and reacetalization effected the epimerization and gave the more stable *trans*-acetal **7**.

Saponification of **7** (1.5 equiv of NaOH, room temperature) and iodolactonization (2.5 equiv of KI_3 at pH 8, 24 h at room temperature) gave an oily iodo lactone **9**: 93%, IR ($CHCl_3$) 1780 cm^{-1}, NMR ($CDCl_3$, 200 MHz) δ 5.09 (dd, J = 7.15 Hz, J = 3.4 Hz, 1 H), 4.46 (d, J = 6.86 Hz, 1 H), 4.26–4.1 (m, 1 H), 3.39 (s, 3 H), 3.34 (s, 3 H), 3.01–2 (m, 6 H). Similarly the *cis*-acetal was converted into the corresponding iodo lactone **10**, 62%, mp 73.5–74 °C. The structure and stereochemistry of the crystalline lactone **10** was firmly established by an X-ray diffraction analysis.[9] Both iodo lactones **9** and **10** have been independently prepared by an elegant but rather long route from 1,5-cyclooctadiene.[10]

Thus the iodo lactone **9** is available in four steps from cyclopentadiene. As already shown by Paquette et al.,[10] it represents a common intermediate for the synthesis of several classes of prostaglandins. Thus, the conversion of **9** to the unsaturated

(6) Ghosez, L.; Montaigne, R.; Roussel, A.; Van Lierde, H.; Mollet, P. *Tetrahedron* **1971**, *27*, 615.

(7) The structure was solved by MULTAN 76 (Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P. MULTAN 76: A System of Computer Programmes for the Automatic Solution of Crystal Structures from X-ray Diffraction Data; York, England, and Louvain-La-Neuve, Belgium, 1976) and refined by the program of Ahmed (Ahmed, F. R.; Hall, S. R.; Pippy, M. E.; Huber, C. P. N.R.C. Crystallographic Programs for the IBM/360 System; National Research Council, Ottawa, Canada, 1966) on the basis of 837 observed reflections for which $I > 2.5\sigma(I)$. Incident radiation was Cu Kα(λ = 1.5148 Å). The final R value is 0.072. Crystal data: $C_9H_9O_3Cl$; monoclinic; space group $P2_1/n$; cell dimensions a = 8.040 (3), b = 15.616 (5), c = 7.416 (3) Å; β = 95.77 (2)°; V = 926.4 Å^3; Z = 4. Coordinate and molecular dimensions are available from the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Chambridge CB2 1EW.

(8) For leading references: Ghosez, L.; O'Donnell, M. J. *Org. Chem.* (*N.Y.*) **1977**, *35-II*, 79.

(9) The structure was solved by the Patterson method and refined by the SHELX 76 program (Sheldrick, G. M. SHELX 76: Program for Crystal Structure Determination; University of Cambridge, England, 1976) Incident radiation was Cu Kα(λ = 1.5418 Å). The final R value is 0.099 for 1180 observed reflections. Crystal data: $C_{10}H_{15}O_4I$; orthorhombic, space group $P2_12_12_1$; cell dimensions a = 11.723 (4), b = 15.752 (5), c = 6.377 (3) Å; V = 1177.6 Å^3; Z = 4.

(10) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972.

(11) Corey, E. J.; Weinshenker, M. M.; Schaff, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

lactone **11** (1.5 equiv of DBU, THF, 2 h, reflux) opens a route toward prostaglandins of the A series.[11] Treatment of **11** with *N*-bromoacetamide (1.2 equiv, aqueous acetone, 20 °C) yielded regio- and stereoselectively the bromohydrin **12** (83%, mp 76–77 °C) which was transformed (phenylbenzoyl chloride in pyridine then debromination with tri-*n*-butyl hydride) into a known[12] precursor **13** of F and E prostaglandins.

Thus, the vicinal alkylation of cyclopentadiene with (carbomethoxy)chloroketene has opened a general and extremely practical route to the prostaglandin hormones and their analogues. In our opinion the outstanding features of this synthesis are (a) *low cost* of starting material and reagent; (b) *high convergence*: two steps lead to the intermediate **4** common to virtually all classes of prostaglandins; therefore, the method is well suited for the preparation of analogues, even of the cis series; (c) *shortness*: e.g., six isolated steps from cyclopentadiene and **2** to the derivative of Corey aldehyde **13**; (d) *high stereoselectivity*; (e) possibility of an *early resolution*, e.g., on the acid derived from **7**.

Acknowledgment. This work was supported by the "Ministère de la Politique Scientifique" (Grant 79/84-13), the "Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture" (fellowships to P.V. and C.H.), and the "Ministère de la Culture Francaise" (fellowship to S.G.). We thank Professor L. Paquette for providing copies of NMR spectra and making available to us a preprint of the full account of his synthesis of prostaglandins.

Supplementary Material Available: Crystallographic data for compounds **3** and **10** (4 pages). Ordering information is given on any current masthead page.

(12) Brown, E. D.; Clarkson, R.; Leeney, T. J.; Robinson, G. E. *J. Chem. Soc. Perkin Trans. 1* **1978**, 1507.

Stereospecific Total Synthesis of 11(*R*)-HETE (2), Lipoxygenation Product of Arachidonic Acid via the Prostaglandin Pathway

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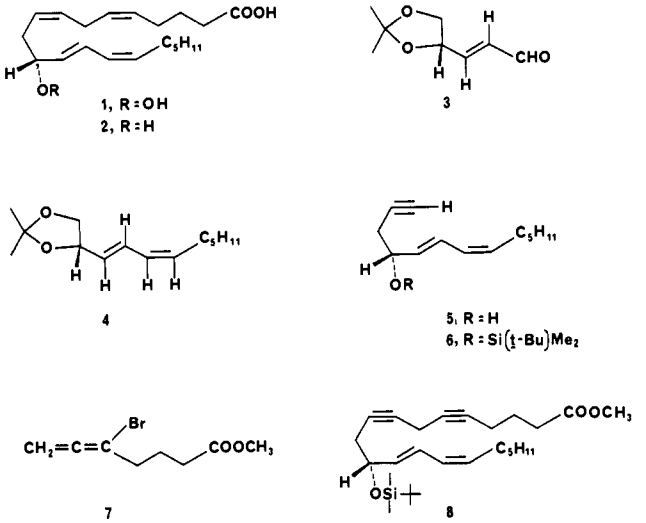
The initial step in the biosynthesis of prostaglandins is the oxidation of arachidonic acid by the 11(*R*)-lipoxygenase pathway to form the hydroperoxide **1**, 11(*R*)-HPETE, or the corresponding peroxyl radical.[1] The related 11(*R*)-hydroxy acid, 11(*R*)-HETE (**2**), which accompanies **1** as a coproduct (Chart I),[2] has been little studied despite the enormous level of research on the chemistry and synthesis of prostaglandins and the great interdisciplinary interest in biosynthetic matters.[3,4] We have been concerned recently with the development of a synthetic process which would make these key compounds readily available for chemical and biological studies. Reported herein is the first synthesis of 11-(*R*)-HETE (without the need for resolution) which is at the same time stereocontrolled, convergent, and illustrative of novel synthetic methodology. The process is applicable as well to the synthesis

Chart I



of 11(*S*)-HETE, and to the preparation of 11-HPETE, using the methodology previously described for the synthesis of 5- and 15-HPETE from the corresponding HETE's.[3,5]

The acetonide of D-glyceraldehyde (prepared from D-mannitol[6,7]) was converted into the *trans*-enal **3** in 75% overall yield by the following sequence: (1) reaction with 1 equiv of lithium ethoxyacetylide in tetrahydrofuran (THF) at −78 °C for 2 h and from −78 to 0 °C for 1 h; (2) hydrogenation (1 atm) of the acetylenic carbinol [obtained by extractive (basic) isolation] to the dihydro derivative using palladium-on-calcium carbonate catalyst (Lindlar) in hexane containing triethylamine (25 °C; reaction monitored by thin layer chromatography, TLC); (3) treatment of this product in wet methylene chloride with a trace of methanesulfonic acid at 25 °C for 30 min.[8] Wittig reaction of enal **3** with the ylide from *n*-hexyltriphenylphosphonium iodide and sodium methylsulfinyl carbanion in dimethyl sulfoxide[9] at 10 °C provided the *trans,cis*-diene **4** in 79% yield (UV_{max} in hexane at 235 nm). Transformation of **4** to the acetylenic carbinol **5** was accomplished in 62% overall yield by the following sequence: (1) deketalization (0.005 N HCl in 4:1 acetonitrile–water at 23 °C for 26 h); (2) monotosylation at primary hydroxyl using 1 equiv of tosyl chloride in pyridine at −20 °C; (3) oxirane closure using 1,8-diazabicyclo[5.4.0]undec-7-ene in THF at 23 °C for 24 h; (4) reaction with lithium acetylide ethylenediamine complex (Aldrich Chemical Co.) at −20 °C in 3:1 hexamethylphosphoric triamide (HMPA)–THF (HMPA) THF for 12 h. Reaction of **5** with *tert*-butyldimethylsilyl chloride–imidazole in dimethylformamide at 25 °C for 4 h provided the corresponding silyl ether **6** in 94% yield. The ethynylation reaction used to prepare the homopropargylic alcohol **5** is noteworthy for its unprecedented position selectivity at the *nonallylic* position which depends on the use of HMPA as cosolvent. This methodology complements the use of organocopper reagents which favor allylic attack.

The completion of the 20-carbon chain was effected by a new and highly selective procedure for carbon–carbon bond formation with generation of a 1,4-diyne unit. While the coupling of a nucleophilic acetylide with a propargylic halide leads to allene

(1) See: Hamberg, M.; Svensson, J.; Wakabayaski, T.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 345 and references cited therein.
(2) See: Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1967**, *242*, 5344.
(3) In a previous paper from these laboratories the concurrent synthesis of (±)-11- and (±)-12-HETE from 11,12-epoxyarachidonic acid has been described: Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.
(4) For nonselective oxidation of arachidonic acid by Cu^{2+}–H_2O_2 and singlet oxygen see: (a) Baeynaems, J. M.; Oates, J. A.; Hubbard, W. C. *Prostaglandins* **1980**, *19*, 87. (b) Porter, N. A.; Wolf, R. A.; Pagels, W. R.; Marnett, L. J. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 349. The latter paper also deals with the question of whether **1** or the corresponding peroxyl radical (or both) are predecessors of prostaglandins.
(5) Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 1435.
(6) Baer, E. *Biochem. Prep.* **1952**, *2*, 31. Baer, E.; Fischer, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463.
(7) For a synthesis of the acetonide of L-glyceraldehyde (starting material for 11(*R*)-HETE), see: Baer, E.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1939**, *61*, 761.
(8) Satisfactory infrared, ultraviolet, proton magnetic resonance, and mass spectral data were obtained on chromatographically purified samples of each intermediate. All reactions were conducted under an atmosphere of argon, and intermediates were stored under argon in frozen benzene at −20 °C or below. All intermediates were obtained as colorless liquids.
(9) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

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