7 8

9 10

11 12

defined by the enolate configuration; the (*E*)-enolates produce the threo aldols selectively, and the (*Z*)-enolates afford the erythro isomers as the major product. On the other hand, reaction of the TAS enolates is characterized by the great negative charge buildup in the transition state (note that in the pericyclic transition-state **7** the charge is neutralized as a whole) and the absence of any cationic species capable of assembling the enolate anion and an aldehyde substrate. As a consequence, the extended transition states of type **8**[16-19] would be favored, since the electrostatic repulsion of the negatively charged oxygens is minimized through such atomic arrangement. We consider that the observed unique stereochemical outcome, *a moderate to very high level of erythro selection which is independent* of enolate geometry, indicates the operation of the mechanism involving the extended transition states.[17,19-21] In the case of the (*E*)-enolates, the transition-state **9** leading to the erythro aldol is favored over the diastereomeric threo transition-state **10**, because the latter suffers repulsive gauche R/R^2 interaction. The erythro transition-state **11** arising from a (*Z*)-enolate is stabilized relative to the threo transition-state **12** for the same reason.

Supplementary Material Available: Spectral and analytical data for the new compounds (1 page). Ordering information is given on any current masthead page.

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(14) Ti^{4+}: (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029.

(15) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

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(17) Murata, S.; Suzuki, M; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

(18) Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* **1979**, *101*, 7723.

(19) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

(20) Heathcock described the involvement of the extended transition state in the reaction of an onium enolate[6a] but withdrew this postulate later.[9]

(21) The mechanism of aldol reaction of zirconium enolates is in controversy. See: (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. (b) Yamamoto, Y.; Maruyama, K. *Ibid.* **1980**, *21*, 4607.

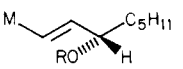
A Triply Convergent Total Synthesis of *l*(-)-Prostaglandin E_2[1]

R. E. Donaldson† and P. L. Fuchs*‡

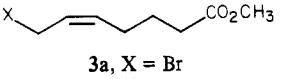
Department of Chemistry, Purdue University
West Lafayette, Indiana 47907

Received December 1, 1980

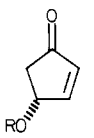
A highly desirable strategy for the synthesis of PGE_2 (**1**) involves a "triply convergent" approach. Formation of the C_{12}-C_{13} bond *and* the C_7-C_8 bond by the sequential addition of the easily available reagents **2**[2] and **3**[3] to a suitably activated, optically active



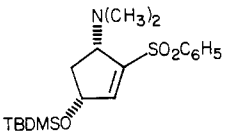
2a, M = Li
b, M = CuR
c, M = AlR_3
d, M = $Zr(Cp)_2Cl$



3a, X = Br
b, X = I



4



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cyclopentene nucleus would constitute such a process. A substantial effort has been invested in using 4-alkoxycyclopent-2-enone (**4**) as the acceptor for such a conjugate-addition/alkylation sequence.[4] Although the conjugate-addition reaction (**2** + **4**) works well, subsequent enolate alkylation with the "upper side chain" reagent **3** is totally unsatisfactory.[4] At present, only indirect procedures are available for further elaboration of the resulting enolate to prostaglandin E_2 (**1**).[4] A general solution to this problem is now available through the use of chiral vinyl sulfone **5** as a substrate for the conjugate-addition/alkylation reaction.

Reaction of the optically active sulfide alcohol **6** [mp ca. 28 °C, $[\alpha]^{25}_D$ +116° (*c* 0.308, $CHCl_3$), 92% ee][5-9] with 3 equiv of

†Graduate Research Associate.
‡A. P. Sloan Fellow, 1977-1979.

(1) Syntheses Via Vinyl Sulfones. 5. For paper 4, see J. Ponton, P. Helquist, P. C. Conrad, and P. L. Fuchs, *J. Org. Chem.*, **46**, 118 (1981).

(2) The chiral 15-(*S*)-*trans*-vinyl iodide precursor (prostaglandin numbering) to organolithium reagent **2a** is available either by classical resolution of the *trans*-halovinyl alcohol [A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Amer. Chem. Soc.*, **94**, 7827 (1972)] or, more recently by enantioselective reduction of the *trans*-iodovinyl ketone with a chiral hydride reducing reagent [R. Noyori, I. Tomino, and M. Nishizawa, *J. Am. Chem. Soc.*, **101**, 5843 (1979)].

(3) (a) J. W. Patterson, Jr. and J. H. Fried, *J. Org. Chem.*, **39**, 2506 (1974); (b) J. Martel and E. Toromanoff, (Roussel-UCLAF), German Patent 2 121 361, 1970; (c) We thank Dr. Patterson for providing us the details of the experimental preparation for this material.

(4) For an in-depth discussion of the problem see (a) R. Davis and K. G. Untch, *J. Org. Chem.*, **44**, 3755 (1979); (b) J. Schwartz, M. J. Loots, and H. Kosugi, *J. Am. Chem. Soc.*, **102**, 1333 (1980).

(5) The racemic sulfide alcohol may easily be prepared on a *5-mol* scale by the method of Evans, Crawford, Fujimoto, and Thomas [*J. Org. Chem.*, **39**, 3176 (1977)].

(6) Evans and Thomas have developed a practical method for the resolution of alcohol **6** as its α-phenethylurethane derivative.[7] They have also assigned the absolute stereochemistry of the two enantiomers of alcohol **6**. [R. C. Thomas, Ph.D. Thesis, University of California, Los Angeles, CA, 1976.] We are very grateful to Professor Evans bringing this resolution procedure to our attention.

(7) Cleavage of the urethane is accomplished by the excellent procedure of Pirkle and Hauske [*J. Org. Chem.*, **42**, 2781 (1977)]. This method allows >90% recovery of the chiral α-phenethyl isocyanate for recycle purposes.

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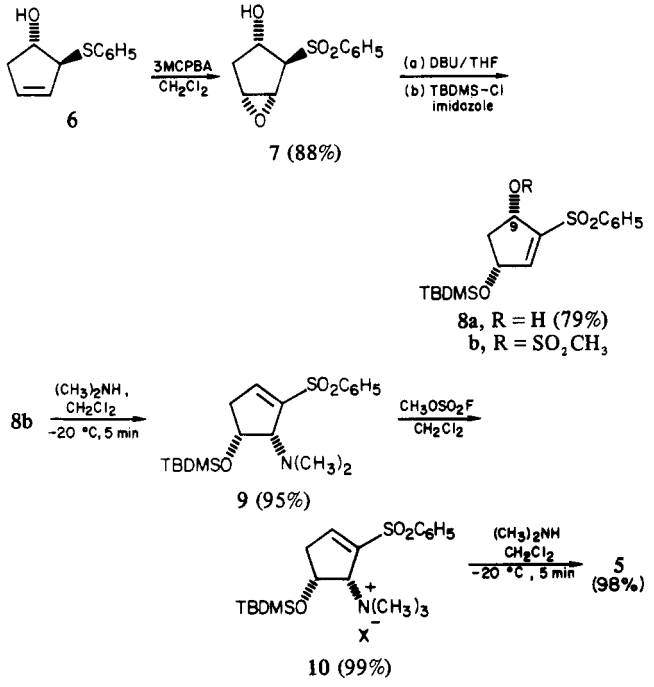
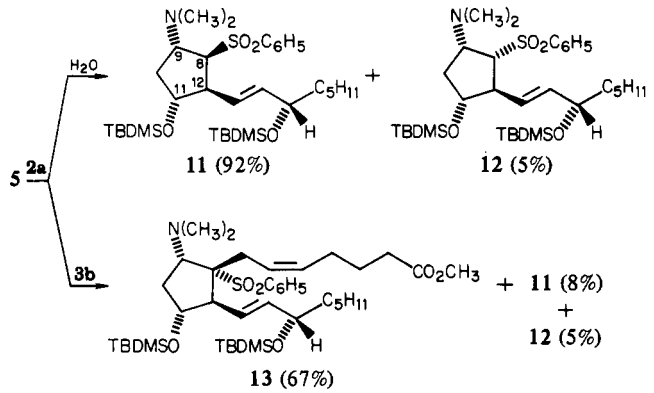
Scheme I

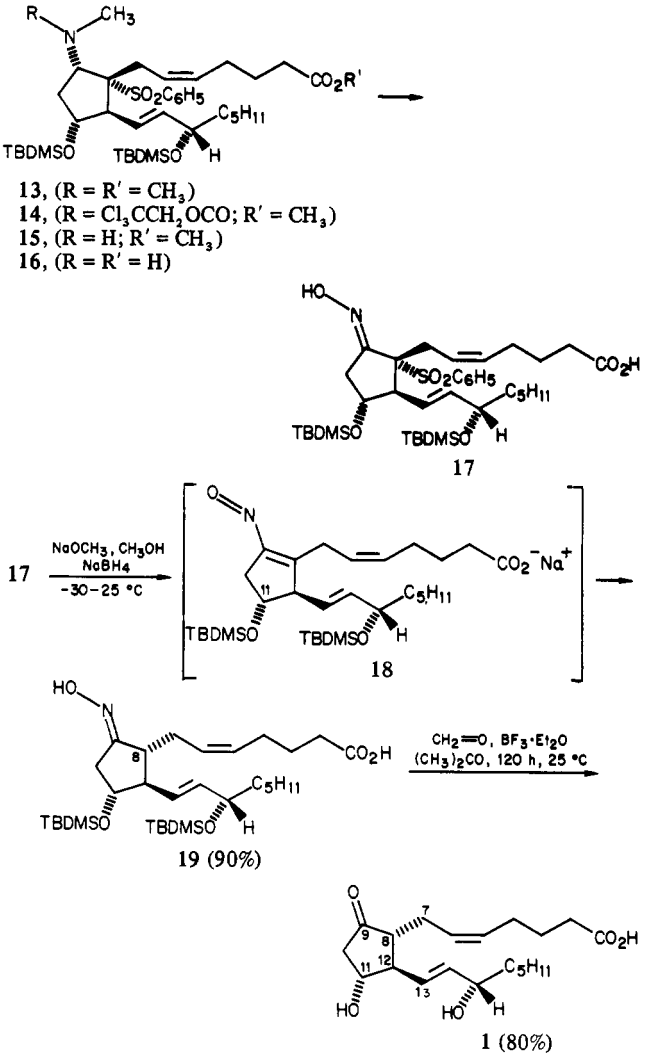


Scheme II



m-chloroperbenzoic acid in methylene chloride smoothly affords the highly crystalline epoxy alcohol **7** [mp 103–104 °C, $[\alpha]^{25}_D$ +64° (*c* 0.429, $CHCl_3$), 88%] (Scheme I). Treatment of **7** with catalytic DBU (to produce the dihydroxyvinyl sulfone) followed by in situ silylation of the less hindered alcohol moiety yields crystalline monosilyl ether **8a** [mp 72–73 °C, $[\alpha]^{25}_D$ +58° (*c* 0.456, $CHCl_3$), 79%].[8,10] Conversion of **8a** to vinyl sulfone **5** was readily accomplished in the following manner: Treatment of alcohol **8a** with methansulfonyl chloride and triethylamine in methylene chloride[11] smoothly affords allylic mesylate **8b**.[8] Although this sensitive material can be successfully isolated and characterized, it was found to be more expedient to simply treat a methylene chloride solution of crude mesylate **8b** with gaseous dimethylamine at −20 °C (5 min) to produce vinyl sulfone **9** [mp 96–98 C, $[\alpha]^{25}_D$ −18° (*c* 0.434, $CHCl_3$), 95%].[8] Quaternization of **9** with methyl fluorosulfonate (1.1 equiv, 2 h, 25 °C, CH_2Cl_2) afforded the crystalline ammonium salt **10**[8] which was also not routinely isolated but rather directly treated with gaseous dimethylamine at −20 °C in methylene chloride (5 min) to yield the crystalline vinyl sulfone **5**[8] [mp 67–68 °C, $[\alpha]^{25}_D$ +153° (*c* 0.385, $CHCl_3$), 98%]. Use of dimethyl sulfate (4 days, 25 °C, CH_2Cl_2) in place of methyl fluorosulfonate gave slightly lower yields (ca. 90%).

Scheme III



Reaction of vinyl sulfone **5** with optically active vinyllithium reagent **2a**[2] (Scheme II) followed by quenching with water provides a 92:5 mixture of 1:1 adducts **11** and **12**.[8,12] Sequential treatment of **5** (28.6 g, 75 mmol) with optically active vinyllithium reagent **2a**[2] (1.1 equiv, THF, −78 °C) followed by warming the mixture to −40 °C, rapidly adding allyl iodide **3b**[3,13,14] (1.1 equiv, as a 0.5 M THF solution), and allowing the reaction mixture to warm to 0 °C over the course of 1 h affords a mixture of products. The mixture is passed through a plug of alumina (to remove nonpolar impurities related to the side-chain reagents **2a**, **3b**) followed by crystallization of the polar fraction from aqueous methanol to afford the nicely crystalline adduct **13**[8,15] [38.7 g, mp 60–62 °C, $[\alpha]^{25}_D$ −20.0° (*c* 0.429, $CHCl_3$), 67%]. Further examination of the polar fraction of the reaction residues reveals

(8) All new compounds had spectra (IR, ^1H NMR, and ^{13}C NMR spectra as well as low- and high-resolution mass spectra in accord with the assigned structures. In addition, a satisfactory combustion analysis was obtained for all crystalline compounds. Yields refer to isolated material for >95% purity.

(9) See J. C. Saddler, R. E. Donaldson, and P. L. Fuchs, *J. Am. Chem. Soc.*, following paper, for conversion of the "unnatural" levorotatory enantiomer of alcohol **6** to chiral vinyl sulfone *l*-**5** in 46% overall yield.

(10) Attempts to directly utilize **8a** (or the enone produced by oxidation of **8a**) in conjugate-addition/alkylation reaction reactions were uniformly unsuccessful. These reactions will be subsequently detailed in a full paper.

(11) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

(12) Both **11** and **12** can be converted to the same product either by reductive desulfonylation or by 1,2 reduction of the β-amino sulfone moiety, indicating that they are isomeric only at C-8. A very minor (1%) product can also be isolated from this reaction which has tentatively been assigned the α configuration at C-12.

(13) The allyl iodide **3b** is prepared from allyl bromide **3a** by rapid exchange with anhydrous sodium iodide in acetone (<10 min). Longer reaction times produce appreciable amounts of the *trans*-allyl iodide.

(14) The use of allyl bromide **3a** in place of allyl iodide **3b** in this reaction also affords **11** (15%), **12** (4%), and **13** (54%).

(15) The structure of **13** was confirmed by X-ray crystallography. We thank Professor S. Byrn and A. T. McKenzie of the Purdue University Department of Medicinal Chemistry and Pharmacognosy for providing this data. This X-ray data will be subsequently reported in our full paper on this subject.

the presence of minor amounts of the nonalkylated 1:1 adducts **11** and **12**.

Reaction of **13** with trichloroethyl chloroformate[16] (2 equiv, 25 °C, 72 h) in the presence of solid sodium bicarbonate yields the urethane **14** as an oil (96%).[8] Reduction of **14** with activated zinc in tetrahydrofuran[17] affords the crystalline secondary amine **15** [mp 50–52 °C, $[\alpha]^{25}_D$ −6.2° (*c* 0.431, $CHCl_3$), 92%]. Hydrolysis of the ester moiety of amine **15** by treatment with sodium hydroxide (3 equiv) in 2% aqueous methanol for 48 h at 25 °C followed by evaporation of the methanol and extraction of a sodium bicarbonate buffered solution with ethyl acetate produces amino acid **16**[8] as a yellowish foam (99%). Addition of 40% peracetic acid (6 equiv) to a solution of **16** in wet methanol containing solid sodium carbonate (15 equiv) and a catalytic amount of sodium tungstate yields the oily α-oximino sulfone **17**[10] (85%) after purification by chromatography on silica gel (Scheme III).[18]

Oximino sulfone **17** is readily desulfonylated by sequential treatment with sodium methoxide (1.0 equiv, −30 °C in methanol, to deprotonate the carboxylic acid moiety), followed by excess sodium borohydride (16 hydride equivalents, warming to 25 °C), and finally slow introduction (1 h) of an additional portion of sodium methoxide (1.2 equiv in methanol) followed by reaction for an additional 5 h at room temperature. Filtration of the crude product through silica gel to remove polar impurities affords the oily oxime **19**[8] (90%) as a single C-8 isomer as assayed by ^{13}C NMR. The desulfonylation reaction presumably occurs via 1,4 addition of hydride to vinyl nitroso intermediate **18** which is produced by base-catalyzed 1,4 elimination of phenylsulfinic acid from the starting α-oximino sulfone **17**.[8,19,20] The very high stereospecificity observed in this reaction may be a consequence of enhanced α-face shielding afforded by a folded conformation of the hydrophobic alkyl groups of the C-11 silyloxy moiety.[21]

Conversion of oxime **19** to chiral prostaglandin E_2 (**1**) is accomplished by reaction of **19** (14.15 g, 25 mmol) with a 1:1 solution of acetone and aqueous 40% formaldehyde[22] in the presence of boron trifluoride (0.7 equiv) as a catalyst for 5 days at 25 °C.[23,24] The crude product was purified by extraction of an ether solution with saturated sodium bicarbonate followed by regeneration of the prostaglandin acids by acidifying the aqueous phase with acetic acid to pH 5.5 (after removal of the ether-soluble paraformaldehyde residues). The *l*(−)-PGE_2 (**1**) was obtained as an oil (6.69 g, 80%)[8] after column chromatography on silica gel to remove a small amount of PGA_2 (ca. 10%). Recrystallization (ethyl acetate/hexane) gave crystalline PGE_2 [mp 64–66 °C, $[\alpha]^{25}_D$ −64° (*c* 1.03, THF)].[25] The identity of PGE_2 was confirmed by 360-MHz ^1H NMR and ^{13}C NMR spectroscopy,[26] as well as by direct comparison with an authentic sample.[27]

Thus, considering the enantioconvergent nature of the process for synthesis of chiral dimethylaminovinyl sulfone *d*-**5**,[9] *the overall yield of l(−)-PGE₂* **1** *from racemic sulfide alcohol dl-6 is 13%, including the resolution process.*[28]

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of early phases of this research (PRF 9941-AC1). We also thank the National Institutes of Health for their generous support of this research (CA-19689 and CA-21840). The ^{13}C NMR used in this investigation was obtained on the departmental CFT-20 instrument provided by NSF Grant 7842. We thank the Purdue University Biological Magnetic Resonance Laboratory (NIH RR01077) for access to the 360-MHz ^1H NMR spectrometer and John Saddler for providing those spectra.

(16) T. A. Montzka, J. D. Matiskilla, and R. A. Partyka, *Tetrahedron Lett.*, 1325 (1974).
(17) J. L. Isidor and R. M. Carlson, *J. Org. Chem.*, **38**, 554 (1973).
(18) Experiments to oxidatively convert tertiary amine **13** to a C-9 ketone were substantially less successful. These will be subsequently detailed in the full paper.
(19) Vinyl nitroso and vinyl azo species have been shown to be powerful acceptors of nucleophiles in similar reactions: (a) E. J. Corey, M. Petrizilka, and Y. Ueda, *Tetrahedron Lett.*, 4343 (1975); (b) C. E. Sacks and P. L. Fuchs, *J. Am. Chem. Soc.*, **97**, 7372 (1975); (c) P. L. Fuchs, *J. Org. Chem.*, **41**, 2935 (1976).
(20) The oxime stereochemistry of **19** is assigned by ^{13}C NMR [see C. A. Bunnell and P. L. Fuchs, *J. Org. Chem.*, **42**, 2614 (1977)].
(21) The C-8 stereochemistry of oxime **19** was confirmed by independent synthesis of **19** from (−)-PGE_2 by sequential silylation and oximination.
(22) This solution is prepared by briefly heating performaldehyde in water to 100 °C, cooling, and using the resulting colorless supernatant solution which is decanted from a minor amount of residual polymer. Commercial 40% aqueous formaldehyde is less satisfactory.
(23) C. E. Sacks and P. L. Fuchs, *Synthesis*, 456 (1976).
(24) For the **19** → **1** transformation it is not presently known whether the active reagent in the silyloxy cleavage is the boron trifluoride [see D. R. Kelly, S. M. Roberts, and R. F. Newton, *Synth. Commun.*, **9**, 295 (1979)] or aqueous hydrofluoric acid produced under the reaction conditions. [See R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 3981 (1979)].
(25) (a) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.*, **92**, 397 (1970) [$[\alpha]^{25}_D$ −61° (*c* 1.0, THF), mp 65–66 °C]; (b) C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, *ibid.*, **97**, 865 (1975) [$[\alpha]^{25}_D$ −52° (*c* 1.15, THF), mp 62–64 °C]; (c) G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *ibid.*, **94**, 2123 (1972) (mp 66–68 °C).
(26) G. F. Cooper and J. Fried, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 1579 (1973).
(27) We thank Dr. Gordon Bundy of the Upjohn Company for generous comparison samples of PGE_2 and 8-*epi*-PGE_2.
(28) *dl*-**6** → *d*-**6** + *l*-**6** (33% each); *d*-**6** → *d*-**5** (65%), *l*-**6** → *d*-**5** (46%);[9] *d*-**5** → *l*(−)-PGE_2 (36%).

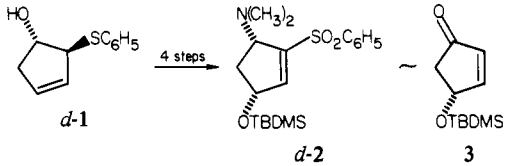
Enantioconvergent Syntheses of Two Classes of Chiral Cyclopentenyl Sulfone Synthons[1]

J. C. Saddler,[†‡] R. E. Donaldson,[†] and P. L. Fuchs*[§]

Department of Chemistry Purdue University
West Lafayette, Indiana 47907

Received December 1, 1980

In the previous paper we described a procedure for conversion of dextrorotatory sulfide alcohol *d*-**1** to chiral aminovinyl sulfone *d*-**2**. Vinyl sulfone *d*-**2** was used as an operational equivalent of



d-**1** *d*-**2** **3**

4-alkoxycyclopentenone (**3**) in a triply convergent, conjugate-addition/alkylation total synthesis of *l*-(−)-prostaglandin E_2.[2]

The resolution of racemic sulfide alcohol **1** was of the classical type and produced approximately equivalent amounts of both enantiometers *d*-**1** and *l*-**1** (ca. 1.6 mol of each, >90% ee from 5 mol of racemic **1**).[3] Conversion of the "unnatural" enantiomer *l*-**1** to prostaglandin precursor *d*-**2** could also be accomplished as follows: Oxidation of *l*-**1** with 1 equiv of *m*-chloroperoxybenzoic

† Graduate Research Associate.
‡ David Ross Fellow, 1978–1980; Texaco Fellow, 1980–1981.
§ A. P. Sloan Fellow, 1977–1979.
(1) Syntheses Via Vinyl Sulfones. 6. For paper 5, see ref 2.
(2) R. E. Donaldson and P. L. Fuchs, *J. Am. Chem. Soc.*, preceding paper in this issue.
(3) See footnote 6 of ref 2 for the details.

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