

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/R² 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.

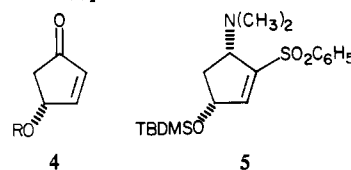
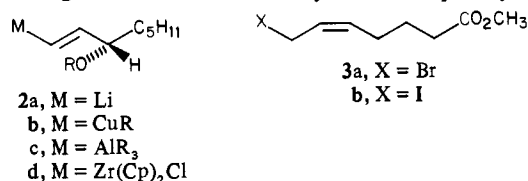
A Triply Convergent Total Synthesis of *1(-)*-Prostaglandin E₂¹

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A highly desirable strategy for the synthesis of PGE₂ (**1**) involves a "triply convergent" approach. Formation of the C₁₂-C₁₃ bond and the C₇-C₈ bond by the sequential addition of the easily available reagents **2**² and **3**³ to a suitably activated, optically active



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 E₂ (**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, [α]_D²⁵ +116° (c 0.308, CHCl₃), 92% ee]⁵⁻⁹ with 3 equiv of

(12) B³⁺: Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. Inoue, T.; Uchimar, T.; Mukaiyama, T. *Ibid.* **1977**, 153. Fenzl, W.; Köster, R.; Zimmermann, H.-J. *Liebigs Ann. Chem.* **1975**, 2201. Masamune, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. Van Horn, D. E.; Masamune, S. *Ibid.* **1979**, 2229. Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979**, 3937. Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

(13) Al³⁺: Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *74*, 373. Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. Nozaki, H.; Oshima, K.; Takai, K.; Ozawa, S. *Chem. Lett.* **1979**, 379.

(14) Ti⁴⁺: (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.

(16) Dubois, J.-E.; Fort, J.-F. *Tetrahedron* **1972**, *28*, 1665.

(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.

[†] 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 2121361, 1970; (c) We thank Dr. Patterson for providing us the details of the experimental preparation for this material.

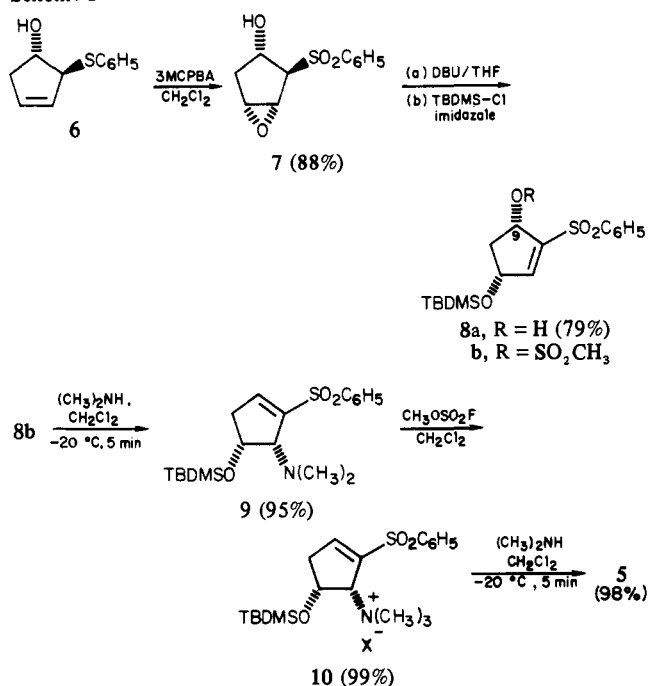
(4) For an in-depth discussion of the problem see (a) R. Davis and K. G. Untch, *J. Org. Chem.*, **44**, 3755 (1979); (b) J. Schwartz, M. J. Loots, and H. Kosugi, *J. Am. Chem. Soc.*, **102**, 1333 (1980).

(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)].

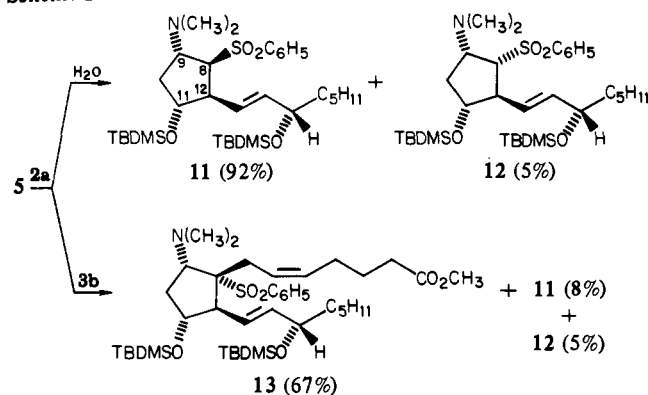
(6) Evans and Thomas have developed a practical method for the resolution of alcohol **6** as its α -phenethylurethane derivative.⁷ They have also assigned the absolute stereochemistry of the two enantiomers of alcohol **6**. [R. C. Thomas, Ph.D. Thesis, University of California, Los Angeles, CA, 1976.]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

Scheme I

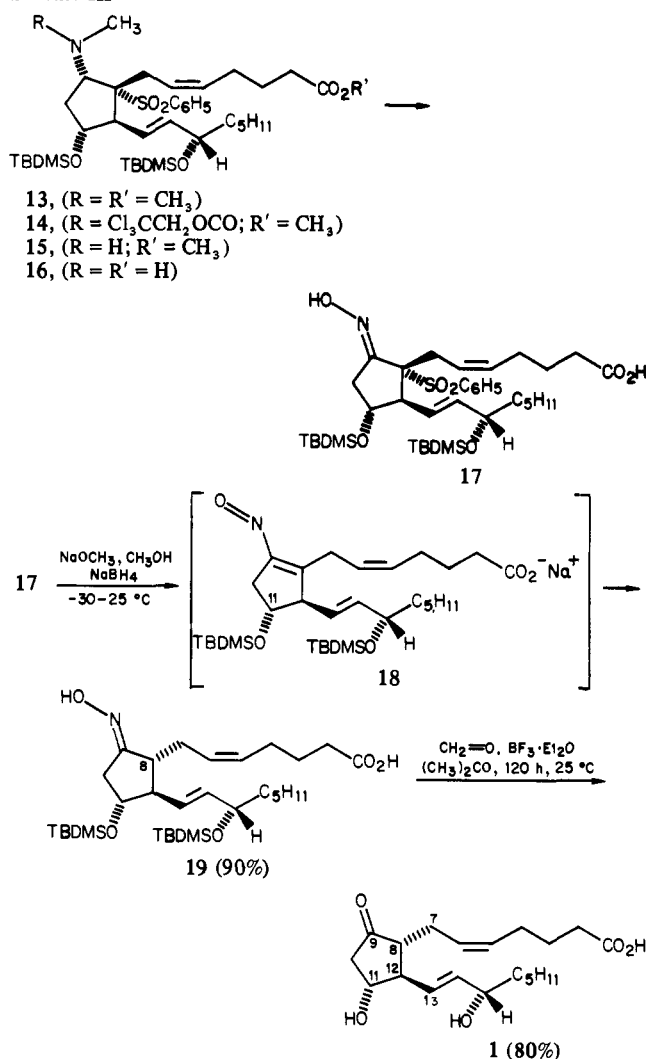


Scheme II



m-chloroperbenzoic acid in methylene chloride smoothly affords the highly crystalline epoxy alcohol 7 [mp 103–104 °C, $[\alpha]_D^{25} +64^\circ$ (*c* 0.429, CHCl₃), 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, $[\alpha]_D^{25} +58^\circ$ (*c* 0.456, CHCl₃), 79%].^{8,10} Conversion of 8a to vinyl sulfone 5 was readily accomplished in the following manner: Treatment of alcohol 8a with methanesulfonyl chloride and triethylamine in methylene chloride¹¹ 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, $[\alpha]_D^{25} -18^\circ$ (*c* 0.434, CHCl₃), 95%].⁸ Quaternization of 9 with methyl fluorosulfonate (1.1 equiv, 2 h, 25 °C, CH₂Cl₂) afforded the crystalline ammonium salt 10⁸ which was also not routinely isolated but rather directly treated with gaseous dimethylamine at

Scheme III



–20 °C in methylene chloride (5 min) to yield the crystalline vinyl sulfone 5⁸ [mp 67–68 °C, $[\alpha]_D^{25} +153^\circ$ (*c* 0.385, CHCl₃), 98%]. Use of dimethyl sulfate (4 days, 25 °C, CH₂Cl₂) in place of methyl fluorosulfonate gave slightly lower yields (ca. 90%).

Reaction of vinyl sulfone 5 with optically active vinyl lithium reagent 2a² (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 vinyl lithium reagent 2a² (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, $[\alpha]_D^{25} -20.0^\circ$ (*c* 0.429, CHCl₃), 67%]. Further examination of the polar fraction of the reaction residues reveals

(12) Both 11 and 12 can be converted to the same product either by reductive desulfonation 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.

(8) All new compounds had spectra (IR, ¹H NMR, and ¹³C 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 1-5 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).

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

Reaction of **13** with trichloroethyl chloroformate¹⁶ (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 tetrahydrofuran¹⁷ affords the crystalline secondary amine **15** [mp 50–52 °C, $[\alpha]^{25}_D -6.2^\circ$ (*c* 0.431, CHCl₃), 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 ¹³C 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 phenylsulfonic 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 E₂ (**1**) is accomplished by reaction of **19** (14.15 g, 25 mmol) with a 1:1 solution of acetone and aqueous 40% formaldehyde²² 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*(–)-PGE₂ (**1**) was obtained as an oil (6.69 g, 80%)⁸ after column chromatography on silica gel to remove a small amount of PGA₂ (ca. 10%). Recrystallization (ethyl acetate/hexane) gave crystalline PGE₂ [mp 64–66 °C, $[\alpha]^{25}_D -64^\circ$ (*c* 1.03, THF)].²⁵ The identity of PGE₂ was

confirmed by 360-MHz ¹H NMR and ¹³C 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 ¹³C 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.

(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 PGE₂ and 8-*epi*-PGE₂.

(28) *dl*-**6** → *d*-**6** + *l*-**6** (33% each); *d*-**6** → *d*-**5** (65%), *l*-**6** → *d*-**5** (46%); *d*-**5** → *l*(–)-PGE₂ (36%).

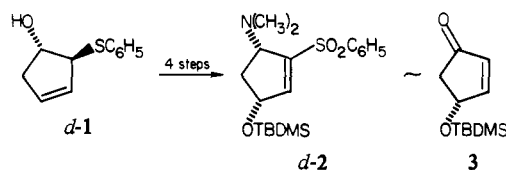
Enantioconvergent Syntheses of Two Classes of Chiral Cyclopentenyl Sulfone Synthons¹

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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



4-alkoxycyclopentenone (**3**) in a triply convergent, conjugate-addition/alkylation total synthesis of *l*(–)-prostaglandin E₂.²

The resolution of racemic sulfide alcohol **1** was of the classical type and produced approximately equivalent amounts of both enantiomers *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

(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 ¹³C 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 (–)-PGE₂ by sequential silylation and oximation.

(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) [$[\alpha]^{25}_D -61^\circ$ (*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) [$[\alpha]^{25}_D -52^\circ$ (*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).

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[§] 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.