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]

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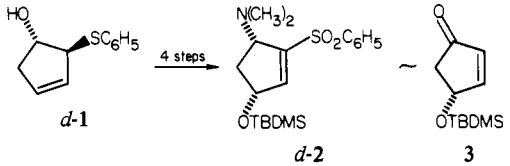
In the previous paper we described a procedure for conversion of dextrorotatory sulfide alcohol *d*-**1** to chiral aminovinyl sulfone *d*-**2**. Vinyl sulfone *d*-**2** was used as an operational equivalent of



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

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(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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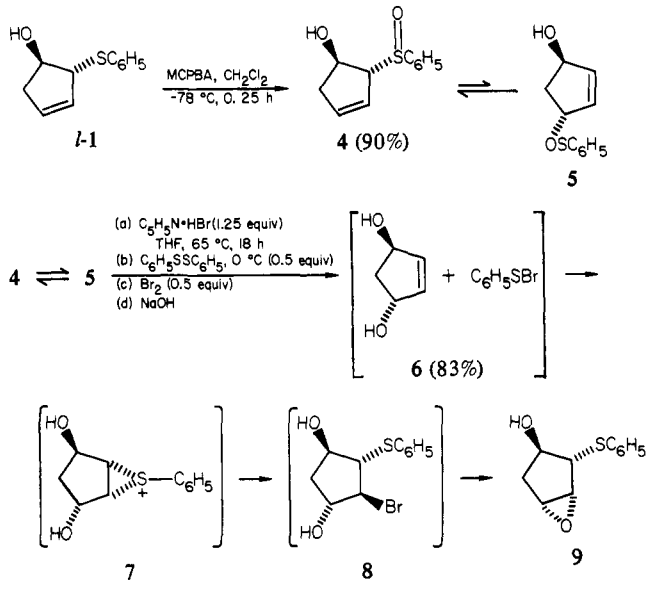
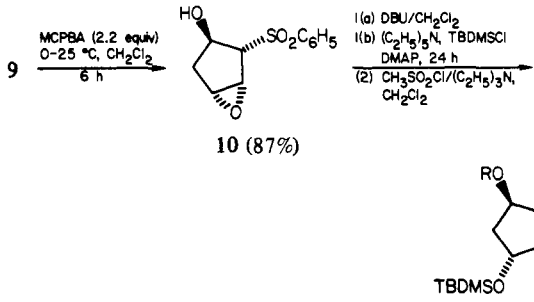
Scheme I



l-1 4 (90%) 5 6 (83%) 7 8 9

oxidation in which the sulfur moiety has been retained in a potentially useful low oxidation state.[8]

Completion of the enantioconversion[9] process was accomplished by MCPBA oxidation of sulfide **9** to the crystalline sulfone **10**

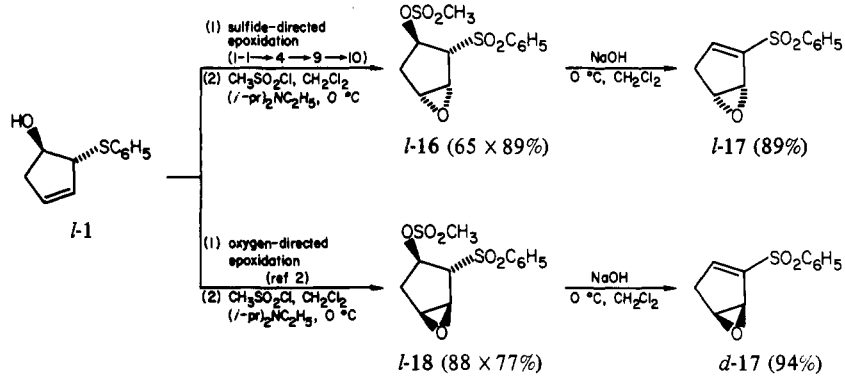


10 (87%)

11, R = H (79%)
12, R = SO_2CH_3

[mp 103.5–105 °C, $[\alpha]^{25}_D$ −137° (*c* 0.437, $CHCl_3$), 87%].[7,10] Treatment (CH_2Cl_2, 0.5 h, 25 °C) of sulfone **10** with a catalytic amount of DBU (0.1 equiv) produces a *trans*-1,4-dihydroxy vinyl sulfone which is monosilylated in situ [$(C_2H_5)_3N$/*t*-Bu-

Scheme II



l-1 *l*-16 (65 × 89%) *l*-17 (89%) *l*-18 (88 × 77%) *d*-17 (94%)

acid (Scheme I) affords sulfoxide **4** which has been shown by Evans to be in equilibrium with sulfenate ester **5**.[4] Treatment of sulfoxide (19.6 g, 94 mmol) **4** with freshly prepared pyridine hydrobromide (1.25 equiv with 10 mol % excess pyridine) in tetrahydrofuran at reflux for 18 h affords a mixture of bromo diol **8** as well as unreacted diol **6** as assayed by thin-layer chromatography.[5] This reaction mixture is cooled to 0 °C, and solid phenyl disulfide (50 mmol) and bromine (50 mmol) was introduced to complete the conversion of diol **6** to bromo diol **8**.[6] It should be noted that sulfenylation of diol **6** from *either* the α or the β face yields a single episulfonium ion (**7**) due to the presence of a C_2 symmetry element in **6**. Bromo diol **8** is quite sensitive and is simply cyclized to the epoxide **9** by treatment with aqueous sodium hydroxide solution in the workup of the sulfenylation sequence. Purification of the crude epoxide was effected by plug filtration through silica gel (to remove excess phenyl disulfide) to afford the oily epoxide **9** (16.3 g, 83%).[7] The overall **4** → **9** transformation is formally a stereospecific sulfide-directed ep-

($(CH_3)_2SiCl$/DMAP (2:1.3:0.2); CH_2Cl_2, 24 h][11] to afford the highly crystalline hydroxy sulfone **11** [mp 76–77 °C, $[\alpha]^{25}_D$ 147° (c 0.360, $CHCl_3$), 79%]. Alcohol **11** was transformed to mesylate **12**[7] by the method of Crossland and Servis.[12] The crude mesylate **12** was not routinely isolated but rather directly treated with gaseous dimethylamine in methylene chloride (−20 °C, 5 min) to afford (dimethylamino)vinyl sulfone **15**[7] [mp 94–95 °C, $[\alpha]^{25}_D$ −17.7° (c 0.434, $CHCl_3$), 92% from **11**] which is identical in every respect with that similarly obtained from cis mesylate **13**[2] which had been prepared from the "natural" enantiomeric sulfide alcohol *d*-**1**.

(4) D. A. Evans, T. C. Crawford, T. T. Fujimoto, and R. C. Thomas, *J. Org. Chem.*, **39**, 3176 (1974).

(5) Addition of sodium hydroxide at this stage affords a 39% yield of epoxy alcohol **9**.

(6) Apparently the pyridine hydrobromide serves to effect *electrophilic* cleavage of sulfenate ester **5** to afford diol **6** and phenylsulfenyl bromide. The need for introduction of excess sulfenyl bromide is probably related to a competitive sulfenylation of pyridine. Use of more hindered pyridine hydrohalides such as that derived from 2,4,6-trimethylpyridine resulted in uselessly long reaction times.

(7) All new compounds exhibit satisfactory ^1H NMR, ^{13}C NMR, mass, exact mass spectra and, in the case of crystalline materials, elemental analysis. Yields refer to isolated material of >95% purity.

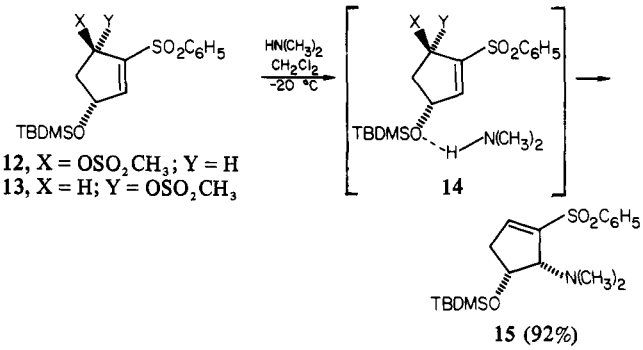
(8) Application of this reaction to the racemic, homologous six-membered ring β-hydroxyallylic sulfide affords a ca. 1:1 mixture of β-(phenylthio)-γ-epoxycyclohexanols (67%) which are diastereomeric at the sulfide-bearing carbon. Sulfide oxidation, mesylation, and 1,2 elimination of *both* of these diastereomers afford a single cross-conjugated epoxyvinyl sulfone in 60% overall yield. The same racemic epoxy vinyl sulfone can be obtained more easily via the oxygen-directed epoxidation route (mp 85–87 °C, 74%).

(9) In its broadest definitional sense, the term "enantioconvergent" refers to a process in which both enantiomers of a racemic substrate are ultimately converted into a single enantiomeric series. The efficiency of such a process will be inversely related to the number of steps between enantiomer separation and enantioconversion. This term was first applied by Trost to an example involving fractional crystallization of a single diastereomeric allylic urethane followed by "enantioconversion" of the crystallization residues by [3.3] sigmatropic rearrangement: B. M. Trost, J. M. Timko, and J. L. Stanton, *J. Chem. Soc., Chem. Commun.*, 436 (1978).

(10) The enantiomer of epoxide **10** has been previously isolated (3% yield) from the crystallization residues of the peracid oxidation of sulfide alcohol *d*-**1** [mp 101–103 °C, $[\alpha]^{25}_D$ +137° (*c* 0.439, $CHCl_3$)].[2]

(11) S. K. Chandhary and O. Hernandez, *Tetrahedron Lett.*, 99 (1979).

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



12, X = OSO_2CH_3; Y = H
13, X = H; Y = OSO_2CH_3

15 (92%)

Apparently the silyloxy group is facilitating a directed addition via intermediate **14** in this polarized S_N2' Lawton-type reaction.[13,14] Conversion of **15** to *d*-**2** (98%) was accomplished as previously described,[2] thus affording an overall yield of 46% from the "unnatural" enantiomer *l*-**1**.

We also find that the enantiomeric sulfide alcohols *l*-**1** and *d*-**1** serve as superb starting materials for providing a pair of enantiomeric cross-conjugated epoxy vinyl sulfones in the context of a separate project directed toward the synthesis of lathrane-type diterpenes.[15] For example, treatment of sulfone alcohol **10** with diisopropylethylamine (1.1 equiv) in the presence of methanesulfonyl chloride (1.2 equiv) in methylene chloride affords the crystalline mesylate *l*-**16** [mp 131–132 °C; $[\alpha]^{25}_D$ −148° (*c* 2.00, $CHCl_3$), 89%].[7] Reaction of *l*-**16** with solid sodium hydroxide (3 equiv) cleanly effects β elimination of the mesyloxy group to generate the epoxy vinyl sulfone *l*-**17** [mp 118–120 °C, $[\alpha]^{25}_D$ −30° (c 1.50, $CHCl_3$), 89%].[7] The enantiomeric epoxy vinyl sulfone *d*-**17** may also be simply prepared from the same sulfide alcohol *l*-**1** (Scheme II). Alcohol-directed epoxidation[2] affords an epoxy alcohol which upon treatment with methanesulfonyl chloride and diisopropylethylamine produces mesylate *l*-**18** [mp 168–171 °C, $[\alpha]^{25}_D$ −39.5[5] (*c* 2.00, $CHCl_3$), 77%].[16] Conversion of *l*-**18** to *d*-**17** [mp 119–121 °C, $[\alpha]^{25}_D$ +29° (*c* 2.00, $CHCl_3$), 94%] via β elimination was accomplished by treatment with excess aqueous 10% sodium hydroxide solution. Naturally, application of the same series of reactions on the enantiomeric sulfide alcohol *d*-**1** ultimately also affords the chiral epoxy vinyl sulfones *d*-**17** and *l*-**17** in an enantioconvergent[9] manner (*d*-**1** → *d*-**16** → *d*-**17**; *d*-**1** → *d*-**18** → *l*-**17**).[15]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (PRF 9941 AC-1, 11617-AC1). We also thank the National Institutes of Health for their generous support of this research (CA-19689, 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 for access to the 360-MHz ^1H NMR spectrometer (NIH RR01077).

(13) For a discussion of the effects of leaving group stereochemistry in the normal S_N2' reaction, see R. M. Magid, *Tetrahedron*, **36**, 1901 (1980), and references contained therein.

(14) For S_N2' reactions of polarized olefins, see (a) S. Mitra and R. G. Lawton, *J. Am. Chem. Soc.*, **101**, 3097 (1979); (b) D. J. Dunham and R. G. Lawton, *ibid.*, **93**, 2074 (1971). See also: (c) R. D. Clark, *Synth. Commun.*, **9**, 325 (1979); (d) R. H. Wollenberg, *Tetrahedron Lett.*, **21**, 3139 (1980); (e) A. B. Smith, III, B. A. Wexler, and J. S. Slade, *Tetrahedron Lett.*, **21**, 3237 (1980). (f) N. H. Cromwell, D. S. Soriano, and E. Doomes, *J. Org. Chem.*, **45**, 4983 (1980); (g) T. Takahashi, K. Hori, and J. Tsuji, *Tetrahedron Lett.*, **22**, 119 (1981).

(15) See J. C. Saddler, P. L. Fuchs, *J. Am. Chem. Soc.*, following paper in this issue for the use of these chiral cross-conjugated epoxyvinyl sulfones.

(16) The relatively poor yield (77%) of mesylate *l*-**18** simply reflects the ease of the *l*-**18** → *d*-**17** transformation. Simply treating crude mesylate *l*-**18** with sodium hydroxide affords an overall yield of 87% from the epoxy alcohol.

Enantiospecific Syntheses of γ-Substituted Enones: Organometallic S_N2' Conjugate-Addition Reactions of Epoxy Vinyl Sulfones[1]

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We have previously shown that γ-oxygenated vinyl sulfones **1a,b**, (R^1 = H) can serve as doubly charge-inverted ynone synthons (**2**).[2] The key reaction involves the conjugate addition of "hard" anions ($pK_a > 25$), such as organolithium species, to vinyl sulfones to yield an α-sulfonyl stabilized anion which is further alkylated in situ. Oxidation of the adducts followed by β elimination of the phenylsulfinic acid affords α,β-difunctionalized enones **3** (R^1 = H) in very good overall yields (Scheme I).[2]

In the context of our efforts directed toward the total synthesis of Lathrane-type diterpenes (**16–18**), we sought to extend this strategy to provide for the enantiospecific incorporation of an additional alkyl moiety (R^1) in the γ position of enone **3**. The specific reaction required involves the S_N2' conjugate-addition reaction of an organometallic species with epoxy vinyl sulfone **4a** (formally a *triply* charge-inverted ynone synthon **5**).

Initial experiments directed toward this goal were not especially encouraging. Treatment of racemic **4a**[3] with methyllithium (1.0 equiv) in THF at −78 °C afforded a mixture of three products after aqueous workup: γ-sulfonylcyclopentenone (**7**)[4,5] (presumably via [1,5] hydrogen migration on the intermediate **6** resulting from γ deprotonation of vinyl sulfone **4a**) as well as a mixture of the conjugate-addition products **8** and **9** in a 4:1 ratio (Scheme II).[4] Additional experimentation revealed that the unwanted deprotonation reaction could be completely avoided and that the relationship between the entering organometallic reagent and the newly forming allylic alcohol moiety could be established in a stereocontrolled fashion. For example, reaction of chiral epoxy vinyl sulfone *l*-**4a**[3] with methyllithium (1.05 equiv) in the presence of lithium perchlorate[6] in a 1:1 mixture of methylene chloride and diethyl ether at −78 °C for 20 min cleanly affords a 95:5 mixture of *d*-**8**/*d*-**9** [$[\alpha]^{25}_D$ = +48.5° (*c* 2.25, $CHCl_3$), 81%].[4,7,8] Alternatively, addition of trimethylaluminum (1.5 equiv in hexane) to a −78 °C suspension of methylcopper (1.5 equiv) followed by epoxy vinyl sulfone *l*-**4a** and slowly warming the reaction to 0 °C over 20 min affords the *anti*-allyl alcohol *d*-**9** [$[\alpha]^{25}_D$ +88° (*c* 2.76, $CHCl_3$), 80%] uncomtaminated with the *syn*-allyl alcohol *d*-**8** within the limits of detection.[4,7,8] Repetition of the last two reactions with the equally readily available dextrorotatory enantiomer of epoxy vinyl sulfone **4a**[3] naturally affords the enantiomers of **8** and **9** (*d*-**4a** → [A] → *l*-**8**; *d*-**4a** → [B] → *l*-**9**). The stereochemical results obtained with these two reactions suggest

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[‡] A. P. Sloan Fellow, 1977–1979.

(1) Syntheses via vinyl sulfones. 7. For paper 6 see ref 3.

(2) (a) P. C. Conrad and P. L. Fuchs, *J. Am. Chem. Soc.*, **100**, 346 (1978); (b) J. C. Saddler, P. C. Conrad, and P. L. Fuchs, *Tetrahedron Lett.*, 5079 (1978).

(3) J. C. Saddler, R. E. Donaldson, and P. L. Fuchs, *J. Am. Chem. Soc.*, preceding paper in this issue.

(4) All new compounds exhibit satisfactory ^1H NMR, ^{13}C NMR, mass, exact mass spectra refer to isolated material of >95% purity.

(5) Although γ-sulfonylcyclopentenone (**7**) and hydroxy dienyl sulfone (**10**) are undesired side products in the context of the study described in this paper, they represent highly functionalized intermediates of obvious synthetic potential. Both **7** and **10** can easily be prepared [**4a** + $(C_2H_5)_3N/(C_2H_5)_3N\cdot HCl/CH_2Cl_2$ → **7**, 65%; **4b** + LDA/THF/−78 °C → **10**, 50%].

(6) E. C. Ashby and S. A. Noding, *J. Org. Chem.*, **44**, 4371 (1979).

(7) MnO_2 oxidation of the 95% pure *d*-**8** yields an enone [$[\alpha]^{25}_D$ −8.7° (*c* 0.70, $CHCl_3$) identical in all respects, except sign of rotation, with that derived from the more pure *d*-**9** [$[\alpha]^{25}_D$ +9.3° (c 0.70, $CHCl_3$)].

(8) The relative stereochemistries of **8**, **9**, and **11**, **12** were assigned by europium shift studies.

0002-7863/81/1503-2112$01.25/0