(neat, NaCl plates) 1823 (m), 1691 (s, cyclobutenyl C=C stretch), 1600 (w), 1495 (m), 1451 (m, aromatic C=C stretch), 1397 (m), 1341 (w), 1325 (m), 1307 (m), 1288 (m), 1268 and 1252 (s, Si–CH_3 deformation), 1222 (s), 1142 (m), 1038 (m), 841 (s, CH_3 rocking), 761 (s, Si–C stretch), 698 (s, monosubstituted phenyl) cm^{-1}; NMR ($CDCl_3$) δ 8.00–6.90 (multiplet, 5 H, aromatic), 2.67–2.26 (two doublets, one centered at 2.50, J_{FH} = 13.40 ± 0.05 Hz, the other at 2.45, J_{FH} = 13.80 ± 0.05 Hz, area ratio 1:3, 2 H, cyclobutene CH_2 for *anti*- and *syn*-$Si(CH_3)_3$ isomers, respectively), 1.34–0.22 (multiplet, 3 H, cyclopropyl), 0.08 (singlet, 9 H, $Si(CH_3)_3$).

***syn*- and *anti*-4-Fluoro-1,5-diphenylspirohex-4-ene.** Freshly distilled styrene (180 mL), the sodium salt from 1.00 g (3.04 mmol) of tosylhydrazone, and 1 equiv of NaH were employed and the irradiation (3.5 h) carried out as described for cyclohexene substrate. Column chromatography on neutral alumina with hexane eluent yielded 540 mg (71.3%) of a mixture of *syn*- and *anti*-4-fluoro-1,5-diphenylspirohex-4-ene as an oil: UV (EtOH) λ_{max} 268 nm (ϵ 3.02 × 10^4); IR (neat, NaCl plates) 1688 (s, cyclobutenyl C=C stretch), 1600 (m), 1494 (s), 1447 (m, aromatic C=C stretch), 1027 (m, cyclopropyl ring deformation), 1940 (w), 1867 (w), 1795 (w), 1735 (w), 760 (s, monosubstituted phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (multiplet 10 H, aromatic), 2.40 (a pair of AB quartets, $J_{FHa} \simeq J_{FHb}$ 13.50 ± 0.05, J_{ab} = 8.90 ± 0.05 Hz, $\Delta\nu_{ab}$ = 0.10 ppm, 2 H, cyclobutene CH_2), 2.44–2.05 and 1.77–1.16 (multiplet, 3 H, cyclopropyl); ^{19}F NMR ($CDCl_3$) δ 91.02 (triplet of doublets, $J_{FH_1} \simeq J_{FH_2}$ 14.02 ± 0.02, J_{FH_3} = 2.10 ± 0.02 Hz, 1F, anti), 98.84 (triplet, J_{FH} = 13.80 ± 0.02 Hz, 1F, syn), ratio of peak areas, *anti*-F–*syn*F = 1:2; mass spectrum (15 eV) parent ion at *m/e* 250, calcd for $C_{16}H_{15}F$, 250.

Competition Experiments. Olefin pairs were employed under the reaction conditions used for single olefins, and the reactivity ratios were determined from the ratios of integrated peak areas in the NMR spectra of product mixtures, normalized for the relative substrate concentrations. Peaks used for the determination of yield ratios were well defined in the spectra of both the pure products and in the product mixtures. The olefin pairs each contained *trans*-2-butene together with 1,3-butadiene, chlorotrifluoroethylene, and trimethylvinylsilane, respectively.

Photolysis of the Tosylhydrazone Salt in Tetrahydrofuran. Dry tetrahydrofuran (180 mL), 1.00 g (3.04 mmol) of tosylhydrazone, and 1 equiv of NaH were employed in a Pyrex jacket surrounding the immersion well. Irradiation (3 h) was carried out as described for cyclohexene substrate. *p*-Tolyl 3-(2-fluoro-1-phenyl)cyclobutenyl sulfone (662 mg, 72.4%) was obtained: mp 135.0–135.5 °C after recrystallization from benzene; UV (EtOH) λ_{max} 217 (ϵ 5.73 × 10^4), 230 (ϵ 4.99 × 10^4), 257 nm (ϵ 6.94 × 10^4); IR (KBr) 3025 (m, C–H stretch), 1592 (m), 1490 (m), 1446 (m, phenyl C=C stretch), 1305 (s), 1152 (m, antisymmetric and symmetric stretch, respectively, of S=O in $-SO_2-$), 816 (m), 732 (s), 618 (w), 474 (m, para-substituted phenyl), 766 (s), 694 (s), 605 (m), 436 (m, monosubstituted phenyl), 559 (s, $-SO_2-$ scissor), 507 ($-SO_2-$ wag), 1325 (s, C–F stretch) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30–7.08 (tolyl AB quartet centered at 7.60, J = 8.8 ± 0.1 Hz $\Delta\nu$-0.49 ppm, and a singlet at 7.30, 9 H, aromatic), 4.55 (quintet of two overlapping triplets, J_{FH} = 6.1 ± 0.1, J_{HH} = 3.1 ± 0.1 Hz, 1 H, CH), 2.64 (doublet of doublets, J_{FH} = 13.8 ± 0.1, J_{HH} = 3.1 ± 0.1 Hz 2 H, CH_2); ^{19}F NMR ($CDCl_3$) δ 92.64 (triplet of doublets, J_{FH_1} = 13.98 ± 0.02, J_{FH_2} 6.23 ± 0.02 Hz); mass spectrum (70 eV) parent ion at *m/e* 302. Anal. Calcd for $C_{17}H_{15}SO_2F$: C, 67.52; H, 5.00. Found: C, 67.35; H, 5.12.

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Registry No.—2-Fluoro-3-phenyl-2-cyclobutenone tosylhydrazone, 56291-31-7; 1,1-dichloro-2,2,4-trifluoro-5-phenylspirohex-4-ene, 67773-55-1; *syn-cis*-1,2-dimethyl-4-fluoro-5-phenylspirohex-4-ene, 67773-56-2; *anti-cis*-1,2-dimethyl-4-fluoro-5-phenylspirohex-4-ene, 67814-61-3; *trans*-1,2-dimethyl-4-fluoro-5-phenylspirohex-4-ene, 67814-62-4; *syn*-spiro[2-fluoro-3-phenyl-2-cyclobutene-1,7′-norcarnane], 67773-57-3; *anti*-spiro[2-fluoro-3-phenyl-2-cyclobutene-1,7′-norcarnane], 67814-63-5; *syn*-4-fluoro-5-phenyl-1-vinylspirohex-4-ene, 67773-58-4; *anti*-4-fluoro-5-phenyl-1-vinylspirohex-4-ene, 67773-59-5; *syn*-1-chloro-1,2,2,4-tetrafluoro-5-phenylspirohex-4-ene, 67773-60-8; *anti*-1-chloro-1,2,2,4-tetrafluoro-5-phenylspirohex-4-ene, 67773-61-9; *syn*-4-fluoro-1-trimethylsilyl-5-phenylspirohex-4-ene, 67773-62-0; *anti*-4-fluoro-1-trimethylsilyl-5-phenylspirohex-4-ene, 67773-63-1; *syn*-4-fluoro-1,5-diphenylspirohex-4-ene, 67773-64-2; *anti*-4-fluoro-1,5-diphenylspirohex-4-ene, 67773-65-3; *p*-tolyl-3-(2-fluoro-1-phenyl)cyclobutenyl sulfone, 67773-66-4; 2-fluoro-3-phenyl-2-cyclobutenone, 771-65-3; 4-toluenesulfonylhydrazine, 1576-35-8; 2-fluoro-3-phenyl-2-cyclobutenone tosylhydrazone sodium salt, 67773-67-5.

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Synthesis of (*R*)- and (*S*)-Epichlorohydrin

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Recently there has been increasing interest in the synthesis of small chiral fragments which can be incorporated with retention of chirality into natural products and compounds of synthetic and medicinal interest.[1] Examples include the synthesis of (*R*)-recifeiolide[2] from (*R*)-methyloxirane[3] and the synthesis of (*S,S*)-vermiculin[4] from (*S*)-(2-bromoethyl)-oxirane.[5] The use of chiral oxiranes is particularly attractive since subsequent reactions do not involve the chiral center. Recognizing the potential importance of such chiral intermediates, we report herein the synthesis of both (*R*)- and (*S*)-epichlorohydrin (chloromethyloxirane).

Epichlorohydrin has been widely used in organic synthesis. Its reaction with nucleophiles yields substituted 2-propanols,[6] 2,3-epoxypropanes,[6] or, in specific cases, heterocyclic compounds.[7] Epichlorohydrin has also found wide application in the field of medicinal chemistry.[8] From these examples, it is apparent that the ready availability of chiral epichlorohydrin would hold great potential in synthetic organic chemistry. Although (*R*)-(−)-epichlorohydrin has been reported,[9] the synthesis, which involves a resolution, is cumbersome and impractical. The reported specific rotation ($[\alpha]^{18}_D$ −25.6°) is also much lower than that which we have observed ($[\alpha]^{23}_D$ −34.3°).

The synthetic scheme (Scheme I) is relatively straightforward and amenable to large scale preparation; however, several points require some comment. The cleavage of the bisacetonide of D-mannitol (1) followed by reduction of the intermediate aldehyde to give 2 has been carried out previously

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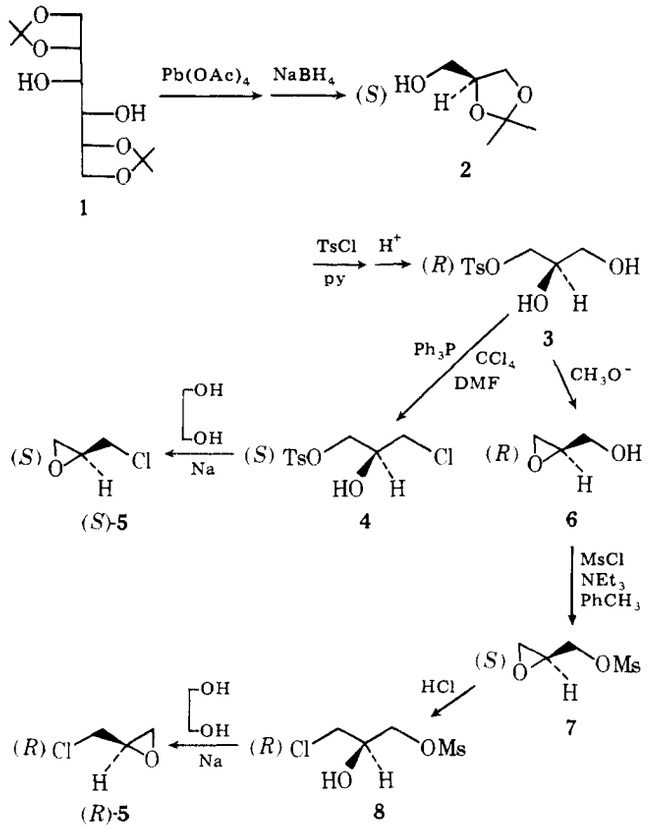
Scheme I



in two different ways: (1) lead tetraacetate cleavage followed by Raney nickel/H_2 reduction[10] and (2) sodium periodate cleavage followed by sodium borohydride reduction.[11] In our hands, the first of these methods was highly variable, apparently due to differences in the quality of commercial Raney nickel. Using the second method, we obtained racemic product in most instances.[12] When the conversion of **1** to **2** was conducted as indicated in the scheme and the sodium borohydride was quenched with ammonium chloride, alcohol **2** of high optical purity was obtained upon distillation.

The key intermediate in the preparation of both chiral epichlorohydrins, (*R*)-3-tosyloxy-1,2-propanediol (**3**), could be obtained in good yield with only slight modifications of the literature procedures.[13] The reaction of **3** with 1 equiv of triphenylphosphine in carbon tetrachloride/DMF[14] gave a mixture containing **4** and triphenylphosphine oxide. The final step in the synthesis of (*S*)-epichlorohydrin (**5**) involved the treatment of **4** with base.

In order to prepare the *R* isomer, the ends of the three carbon unit must be selectively reversed. This could be accomplished by first preparing (*R*)-glycidol (**6**),[13] which was then used in the preparation of **7**.[15] Since initial attempts at the purification of **6** by distillation[13] led to complete decomposition in our hands, crude material[16] was subsequently used. The opening of the oxirane ring of **7** with HCl led to the formation of **8**,[15] an intermediate analogous to **4** in the *S* chiral series. (*R*)-Epichlorohydrin could be readily obtained from **8** via treatment with base.

Some comment should be made regarding the choice of sodium ethylene glycolate as the base for the last step in both synthetic sequences. Several probe reactions were conducted with racemic material using various bases (e.g., NaH, $NaOCH_3$, BuLi, NaOH) in several low-boiling solvents (e.g., CH_2Cl_2, ether, THF, ether/CH_3OH), and extremely poor results were obtained. Examination of the reaction by proton NMR, using sodium in deuteriomethanol, revealed that epichlorohydrin was formed in high yield. Apparently, the removal of large volumes of solvents, even at low temperature, led to significant losses via codistillation. The use of sodium ethylene glycolate allowed for the room temperature distillation of epichlorohydrin directly from the reaction mixture to give good yields of relatively pure material. The overall yield of (*S*)-**5** from **3** was 56%, while (*R*)-**5** was obtained in 50% overall yield.

The chiral purity of each isomer could be determined through an examination of the proton NMR spectrum in the presence of a chiral shift reagent, tris[3-heptafluorobutyryl-*d*-camphorato]europium(III) [Eu(hfbc)$_3$].[17] Assay conditions were arrived at by studying the effect of the addition of the lanthanide reagent on racemic material. In general, 0.1–0.3 molar equiv of Eu(hfbc)$_3$ per mole of epichlorohydrin resulted in 10–30 Hz separation of the enantiomeric signals corresponding to the terminal epoxide protons. The signals derived from (*S*)-**5** were shifted further downfield than those derived from the *R* isomer. When we examined samples of the chiral epichlorohydrins[18] in this manner, we found that (*R*)-**5** exhibited a chiral purity of 97 ± 2% and (*S*)-**5** a chiral purity of 99 ± 1%.

To summarize, the synthesis of (*R*)- and (*S*)-epichlorohydrin (**5**) from the same chiral starting material has been accomplished in good overall yields; the ready availability of these intermediates should make them extremely useful in synthetic organic chemistry. We are currently studying the relative contributions of chloride displacement and epoxide ring opening in the reactions of nucleophiles with chiral epichlorohydrins.

Caution: The potential toxicological hazards of epichlorohydrins have been described.[19]

Experimental Section

NMR spectra were determined in the indicated solvent on a Varian T-60 using tetramethylsilane as an internal standard. The NMR studies to determine chiral purity of the epichlorohydrins were conducted on a Varian SC-300 operating in the Fourier transform mode. Optical rotations were determined using a Perkin-Elmer 141 polarimeter. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Concentration of solutions was accomplished on a Buchi rotary evaporator at water aspirator pressure (20–25 mm).

(*S*)-Glycerol 1,2-Acetonide (2). To an ice-cooled solution of **1** (80.0 g, 0.3 mol) in THF (400 mL) was added portionwise with stirring dry $Pb(OAc)_4$ (134 g, 0.3 mol) while maintaining the temperature below 10 °C. The solution was stirred for 30 min with ice cooling and an additional 30 min without. After filtering through Super-Cel and cooling in an ice bath, a solution of $NaBH_4$ (22.9 g, 0.61 mol) in 4% aqueous NaOH (400 mL) was added dropwise with vigorous stirring while maintaining the temperature below 10 °C. After stirring in an ice bath for 30 min and at room temperature for 90 min, solid ammonium chloride was added to the solution until it buffered at about pH 8. The THF was removed under reduced pressure, and the resulting aqueous solution was saturated with NaCl. After extracting into ethyl acetate, the organic layer was washed with 5% aqueous NaOH saturated with NaCl, dried (Na_2SO_4), and concentrated. Distillation afforded pure **2** (58.4 g, 73%): bp 80–90 °C (20 mm); ^1H NMR ($CDCl_3$) δ 1.35 (3 H, s), 1.45 (3 H, s), 3.5–4.5 (6 H, m); $[\alpha]^{25}_D$ 11.3° (*c* 5.175, CH_3OH).

(*R*)-3-Tosyloxy-1,2-propanediol (3).[13] To an ice-cooled solution of **2** (72.0 g, 0.55 mol) in pyridine (300 mL) was added portionwise with stirring *p*-toluenesulfonyl chloride (104.0 g, 0.55 mol). After standing in a refrigerator for 16 h, the reaction mixture was diluted with ether (300 mL), washed with 1 N HCl until the aqueous wash was acidic, and then washed with saturated aqueous $NaHCO_3$. The ether layer was dried (Na_2SO_4) and concentrated to give (*R*)-3-tosyloxypropanediol acetonide (141.0 g, 91%), which was used without further purification.

The acetonide from above in acetone (100 mL) and 1 N HCl (300 mL) was heated on a steam bath for 30 min. The resulting solution was concentrated to dryness, and the residue was dissolved in CH_2Cl_2. After drying (Na_2SO_4) and concentration, the resulting oil solidified upon standing. Residual solvents were removed at 25 °C and 0.5 mm over 18 h to give **3** (121.0 g, 100%): mp 54–59 °C (lit.[14] mp 61–63 °C);

^{1}H NMR ($CDCl_3$) δ 2.4 (3 H, s), 3.3–4.3 (7 H, m), 7.35 and 7.8 (4 H, 2d, J = 8 Hz); $[\alpha]^{25}_D$ −9.3° (c 4.99, CH_3OH).

(*R*)-Glycidol (6).[13] To an ice-cooled solution of **3** (120.5 g, 0.49 mol) in methanol (200 mL) and ether (100 mL) was added sodium pellets (10.7 g, 0.45 mol) in three portions over approximately 1 h. Stirring was continued with ice cooling for 1 h. The reaction mixture was concentrated at 30 °C, and the residue was taken up in ether. After filtration, the solvent was removed at 30 °C (25 mm), and the residue was treated with chloroform and reconcentrated to remove the last traces of methanol. An additional chloroform treatment as above gave (*R*)-glycidol (**6**; 33.5 g, 93%), which was used without purification in subsequent steps.

A small sample of **6** was obtained by distillation (bp 70 °C, 15 mm) prior to thermal decomposition of crude **6** to give material having the following properties: ^{1}H NMR ($CDCl_3$) δ 3.95 (1 H, d of d, J = 12 and 2 Hz), 3.55 (1 H, d of d, J = 12 and 5 Hz), 3.15 (1 H, m), 2.75 (2 H, m); $[\alpha]^{24}_D$ 16.5° (c 5.88, $CHCl_3$).

(*S*)-3-Mesyloxy-1,2-epoxypropane (7). To an ice-cooled solution of **6** (5.0 g, 0.068 mol) and triethylamine (8.1 g, 0.080 mol) in toluene (100 mL) was added, over 15 min, methanesulfonyl chloride (8.0 g, 0.070 mol) in toluene (25 mL). Stirring was continued with cooling for 1 h. The solution was filtered and concentrated to give an 80–85% yield of the crude product; this material could be used without further purification. Distillation gave **7** (61%): bp 92–95 °C (0.1 mm); $[\alpha]^{22}_D$ 23.7° (c 5.16, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 4.5 (1 H, d of d, J = 12 and 3 Hz), 4.1 (1 H, d of d, J = 12 and 6 Hz), 3.3 (1 H, m), 3.1 (3 H, s), 2.8 (2 H, m).

Anal. Calcd for $C_4H_8O_4S$: C, 31.57; H, 5.30. Found: C, 31.99; H, 5.37.

(*R*)-Epichlorohydrin [(*R*)-5]. Concentrated HCl (20 mL) was added to **7** (5.0 g, 0.033 mol) over 15–20 min. After stirring for an additional 30 min, the water was removed through the addition and subsequent evaporation of ethanol. Finally, residual ethanol was removed at room temperature and 0.1 mm to give **8** (5.4 g, 85%): ^{1}H NMR ($CDCl_3$) δ 4.35 (2 H, d), 4.1 (1 H, m), 3.65 (2 H, d), 3.1 (3 H, s), 2.9 (1 H, broad s); $[\alpha]^{22}_D$ 7.1° (c 5.78, CH_3OH).

To **8** (5.4 g, 0.029 mol) in dry ethylene glycol (20 mL) was added a solution of sodium ethylene glycolate [from sodium pellets (0.8 g, 0.034 mol)] in dry ethylene glycol (20 mL). After stirring for 15 min, (*R*)-epichlorohydrin (**5**) (2.2 g, 86%) was distilled from the reaction mixture at room temperature and 0.2 mm and trapped in dry ice/acetone: ^{1}H NMR ($CDCl_3$) δ 3.6 (2 H, d), 3.2 (1 H, m), 2.8 (2 H, m); $[\alpha]^{22}_D$ −33.0° (c 4.22, CH_3OH).

A small sample was further purified by preparative GC on an HP 5710 A instrument using a 6 ft 5% OV-17 column with an oven temperature of 60 °C to give (*R*)-**5**, $[\alpha]^{23}_D$ −34.3° (c 1.50, CH_3OH).[18]

Anal. Calcd for C_3H_5ClO: C, 38.94; H, 5.45. Found: C, 38.74; H, 5.51.

The chiral purity was determined at concentrations of 0.5–1.0% (w/v) in $CDCl_3$ using chiral Eu(hfbc)$_3$, 97 ± 2% (*R*)-**5**.[18]

(*S*)-Epichlorohydrin [(*S*)-5]. To triphenylphosphine (13.2 g, 0.05 mol) in CCl_4 (20 mL) and DMF (50 mL) was added **3** (12.3 g, 0.05 mol) in DMF (50 mL) all at once. After the addition was complete, the temperature increased to 50 °C over 15 min. The mixture was then allowed to stir for 3 h. The residual solvents were removed (50 °C, 2 mm), and the residue was taken up in H_2O and extracted with CH_2Cl_2. The organic phase was washed again with H_2O, dried (Na_2SO_4), and concentrated. Residual solvents were removed at 25 °C and 0.2 mm over 18 h.

To this residue, composed of triphenylphosphine oxide and (*S*)-**4**, in dry ethylene glycol (50 mL) was added a solution of sodium ethylene glycolate [from sodium pellets (1.25 g, 0.054 mol)] in dry ethylene glycol (50 mL). After stirring for 15 min, (*S*)-epichlorohydrin (**5**) was distilled from the reaction mixture at room temperature and 0.2 mm and trapped in dry ice/acetone. The ^{1}H NMR spectrum indicated that traces of CH_2Cl_2 and H_2O were present, $[\alpha]^{20}_D$ 28.1° (c 2.47, CH_3OH).

A small sample was purified by preparative GC to yield pure (*S*)-**5**, $[\alpha]^{23}_D$ 33.0° (c 1.126, CH_3OH).[18]

Anal. Calcd for C_3H_5ClO: C, 38.94; H, 5.45. Found: C, 38.82; H, 5.81.

The chiral purity was determined at concentrations of 0.5–1.0% (w/v) in $CDCl_3$ using chiral Eu(hfbc)$_3$, 99 ± 1% (*S*)-**5**.[18]

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Registry No.—**1**, 1707-77-3; **2**, 22323-82-6; **3**, 41274-09-3; **4**, 67800-61-7; (*R*)-**5**, 51594-55-9; (*S*)-**5**, 67843-74-7; **6**, 57044-25-4; **7**, 67800-62-8; **8**, 67800-63-9; (*R*)-3-tosyloxypropanediol acetonide, 23788-74-1.

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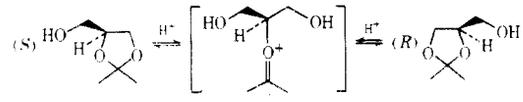
(12) Although earlier workers[11] used crude alcohol **2**, we felt that a purification at this point in the synthesis would be desirable. Crude **2** derived from $NaIO_4$ cleavage and $NaBH_4$ reduction followed by quenching with acetic acid exhibited a good optical rotation, but distillation of this material gave racemic product (**2**). A reasonable mechanism by which a trace acidic impurity (presumably derived from $NaIO_4$) could cause the racemization of (*S*)-**2** is indicated below.



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(14) R. H. Schlessinger and G. S. Ponticello, *Tetrahedron Lett.*, 4361 (1969). Since crude **4** was used in the preparation of (*S*)-**5**, the use of excess CCl_4 without DMF led to the isolation of (*S*)-**5** contaminated with varying amounts of CCl_4. The use of DMF allowed for the removal of most of the contaminating CCl_4 at an earlier stage.
(15) The isolation of **7** and **8** as racemic mixtures has been reported: N. Nakabayashi, E. Masuhara, and Y. Iwakura, *Bull. Chem. Soc Jpn.*, **39**, 413 (1966).
(16) The NMR spectrum of the crude (*R*)-glycidol (**6**) indicated that it was ≥95% pure.
(17) R. R. Fraser, M. A. Petit, and J. K. Saunders, *Chem. Commun.*, 1450 (1971).
(18) Trace impurities in each chiral sample complicated their analyses with Eu(hfbc)$_3$. Therefore, aliquots of both (*R*)-**5** and (*S*)-**5** were purified by preparative gas chromatography as indicated in the Experimental Section. The minor inconsistency between optical rotation and chiral shift NMR data may be due to trace impurities, which cannot be detected in the NMR spectra, in either (*R*)-**5** or (*S*)-**5**, or both.
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A Novel Naphthyridinone Synthesis via Enamine Cyclization

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In a recent paper,[1] we described the use of dimethylformamide dimethyl acetal (DMF acetal) in the synthesis of 4-

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