purple crystals remaining were dried *in vacuo* to afford 24.1 g of crude octaethylporphyrin. Recrystallization from toluene afforded 23.51 g (52%) of pure octaethylporphyrin, mp 324–325° (lit.[4] mp 322°). Use of distilled Mannich base raised the yield to 60–65%. The visible spectrum in benzene is given in Table I.

Registry No.—1, 2683-82-1; 3, 16200-50-3; 6, 16200-52-5; 7, 16200-51-4.

Acknowledgment.—Partial support by the National Institutes of Health and the National Science Foundation is acknowledged.

The Synthesis of the Optically Active Cleland Reagent [(−)-1,4-Dithio-L_g-threitol]

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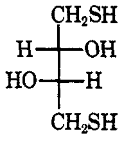
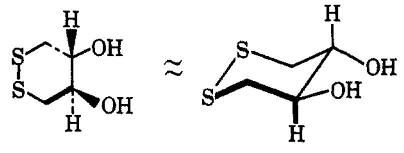
The introduction[2a] of *rac*-dithiothreitol (**1**) as a new reagent for the reduction of disulfide bonds and the protection of thiol groups has proved useful in a growing number of applications to the study of biologically active peptides.[3]

Since the available evidence[4–7] suggests that disulfide bridges in proteins may exist in asymmetric helical configurations which can, in some cases, have right-handed (in some cases left-handed) chirality, it occurred to us that an optically active form of Cleland's reagent should be expected to reduce right-handed and left-handed helical disulfide bridges at different rates, and that if the difference in these rates is sufficiently great, such a reagent would provide extremely interesting new possibilities for stereoselective reduction of individual disulfide bridges in complex molecules.



1, racemic
2, $(R,R) \approx (\text{L}_g)$-(−) isomer
(Rosanoff convention)



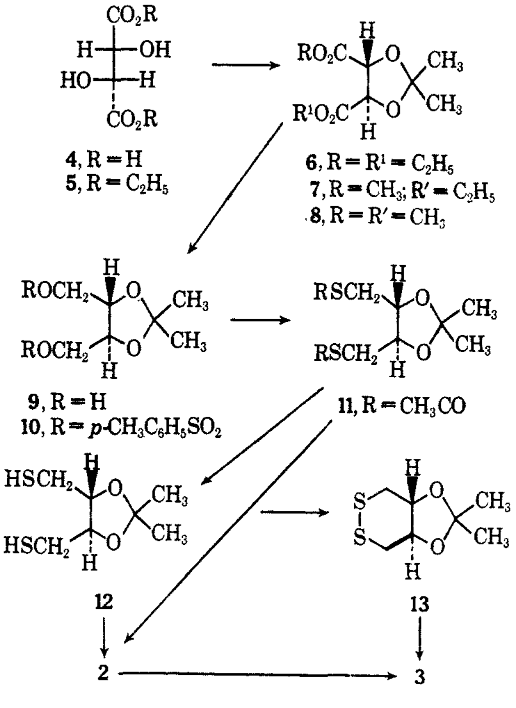
3

This paper describes the synthesis of L_g-(−)-1,4-dithiothreitol (**2**) from L_g-(+)-tartaric acid (**4**), whose absolute configuration was established by a direct X-ray method.[8,9]

We also desired the pure optical isomer of the oxidized form of dithiothreitol, 4,5-dihydroxy-1,2-dithiane (**3**), which has the same absolute stereochemical configurations as L_g-(+)-tartaric acid and could thus provide a reference standard relating the absolute helical sense of an asymmetric disulfide function to its observed circular dichroism (CD)[10] or optical rotatory dispersion (ORD). Compound **3** must have the 4*R*,5*R* configurations at the hydroxyl positions, and, in its presumably more stable chair conformation, would have the disulfide function in a right-handed (or P) helix.[11]

The synthetic reactions are shown in Scheme I. Compounds **4–6** and **8–10** have been described in the literature. Compounds **11–13** have not been previously prepared; racemic, but not optically active, forms of **2** and **3** have been described.

SCHEME I



Diethyl L_g-tartrate (**5**) was converted into the cyclic ketal ester **6** by reaction with 2,2-dimethoxypropane and a small amount of acidic catalyst.[12] Some ester interchange accompanied the formation of **6**, yielding esters **7** and **8**; the total yield of usable ester was nearly quantitative. Less satisfactory procedures for syn-

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[2] (a) W. W. Cleland, *Biochemistry*, **3**, 480 (1964); (b) R. M. Evans, J. B. Fraser, and L. N. Owen, *J. Chem. Soc.*, 248 (1949).

[3] For a recent bibliography of uses, *cf.* "Biologics," No. 50, Calbiochem, Los Angeles, Calif., 1967, p 1.

[4] J. A. Schellman in "Optical Rotatory Dispersion. Applications to Organic Chemistry," C. Djerassi, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Section 15-4.

[5] L. Velluz and M. Legrand, *Angew. Chem. Intern. Ed. Engl.*, **4**, 838 (1965).

[6] S. Beychok, *Science*, **154**, 1288 (1966).

[7] M. Carmack and I. W. Stapleton, unpublished results; *cf.* I. W. Stapleton, Ph.D. Dissertation, Indiana University, 1966, p 149 ff, University Microfilms, Ann Arbor, Mich., Order No. 66–14,894; *Dissertation Abstr.*, **27B**, 4330 (1967).

[8] J. M. Bijvoet, A. F. Peerdeman, and A. J. Bommel, *Nature*, **168**, 271 (1951).

[9] For pertinent comments on the nomenclature relating to the stereoisomers of tartaric acid, *cf.* J. N. Baxter *J. Chem. Educ.*, **41**, 619 (1964), and E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co. Inc., New York, N. Y., 1962, pp 90–96.

[10] M. Carmack and L. A. Neubert, *J. Amer. Chem. Soc.*, **89**, 7134 (1967).

[11] R. S. Cahn, C. Ingold, and V. Prelog. *Angew. Chem. Intern. Ed. Engl.*, **5**, 385, 391, and 406 (1966).

[12] An example of *trans*-ketalization with 2,2-dimethoxypropane has been well described by N. Lorette and W. Howard [*Org. Syn.*, **42**, 1 (1962)].

thesis of **6** have been described.[13a,14] In a further simplification of the procedure, $\mathrm{L_g}$-tartaric acid (**4**) reacted smoothly with 2,2-dimethoxypropane to yield the ester **8**.[13b]

The distilled mixture of esters **6–8** or pure **8** was reduced with lithium aluminum hydride to the glycol ketal **9**.[14] Compound **9** was converted into the ditosylate **10**[15] in high yield.

The replacement of the tosyl groups of **10** with sulfur-containing functions was best accomplished with potassium thiolacetate, which in refluxing ethanol smoothly gave the new compound **11** in good yield.[16] Alternative reagents for sulfur introduction (thiourea, potassium xanthate) gave complex and unsatisfactory replacement reactions. Potassium thiocyanate yielded a clean product, which, however, proved to be unsatisfactory for the remaining steps of the synthesis scheme.

Sodium methoxide in refluxing methanol[17] removed the acetyl groups of **11** to yield the 2,3-*O*-isopropylidene-1,4-dithio-$\mathrm{L_g}$-threitol (**12**) nearly quantitatively.

Oxidation of the isopropylidenedithiothreitol (**12**) with oxygen in methanolic potassium hydroxide gave the crystalline 1,2-dithiane ketal (**13**).

Both **11** and **12** were hydrolyzed in hot dilute hydrochloric acid–methanol. The product, $\mathrm{L_g}$-(−)-1,4-dithiothreitol (**2**), was first obtained as a colorless, viscous liquid after distillation *in vacuo*, but then slowly crystallized on standing and was purified by sublimations at 41° (0.02 mm). The purified (−)-isomer melts at 48.2–49.8°, whereas the *rac*-dithiothreitol has been reported to melt at 40[2a] and 42–43°.[2b]

(4*R*,5*R*)(+)-4,5-Dihydroxy-1,2-dithiane (**3**) was obtained in 93% yield as a colorless, crystalline solid (mp 116.2–117.8°, $[\alpha]^{23}$ °D 260° (chloroform)) when the dithiane ketal (**12**) was hydrolyzed in dilute methanolic hydrochloric acid. Purification could be effected by sublimation or recrystallization. The racemic form was reported to melt at 132[2a] and 130°.[18b] Preparation of the optically active **3** from **2** by ferricyanide oxidation according to the procedure used for racemic **3**[2a] gave a lower yield than by the route from **12**, and the product proved to be more difficult to purify.

The *cis* isomer (*meso*) of the ketal (**13**) has been characterized and its conformational mobility investigated.[18a] The relatively easy ketalization of racemic **3** with cyclohexanone has been observed and commented upon.[18b]

Experimental Section

Melting points were taken in open glass capillaries in a Hershberg apparatus and are uncorrected. Analyses were carried out by Alfred Bernhardt, Max Planck Institut, Mülheim (Ruhr), Germany. Infrared spectra were measured in a Perkin-Elmer Infracord Model 137B. Ultraviolet spectra were recorded in a Jasco Model ORD/UV-5 recording spectrophotometer. Pmr spectra were measured using a Varian A-60 spectrometer. The optical rotations were measured with a Rudolph polarimeter, Model 80, in a 2-dm cell. Vpc work was done in an F & M Model 500 chromatograph using the following columns: A, 10% silicon grease on Chromosorb W; B, 5% Carbowax 20M on Haloport F; and C, 5% Apiezon L on Haloport F.

Diethyl 2,3-*O*-Isopropylidene-$\mathrm{L_g}$-tartrate (6).—A solution containing 105.9 g (0.512 mol) of diethyl $\mathrm{L_g}$-tartrate,[19] 53.9 g (0.615 mol) of 2,2-dimethoxypropane (Aldrich), 200 ml of dry benzene, and 0.25 g of *p*-toluenesulfonic acid monohydrate was refluxed, while the benzene–methanol azeotrope (bp 58°) was slowly removed at the head of a vacuum-jacketed, helix-packed distillation column. After 10 hr the temperature of the refluxing vapor had risen to 77°. The catalyst was neutralized with 0.5 g of anhydrous potassium carbonate; the solvent and unreacted 2,2-dimethoxypropane were removed under reduced pressure, and the product mixture was distilled as 124.5 g of colorless (sometimes light yellow) liquid, bp 85–96° (0.04 mm). Vpc analysis (column A) showed the presence of three high-boiling components. Integration of the chromatogram, as well as integration of the pmr spectrum, showed that the product was a mixture of ester–ketal homologs (**6–8**) in the ratio 77:21:2. (This ratio varied slightly from experiment to experiment.)

Dimethyl 2,3-*O*-Isopropylidene-$\mathrm{L_g}$-tartrate (8).—A mixture of 101 g (0.673 mol) of powdered $\mathrm{L_g}$-tartaric acid (Matheson Co.), 160 g (1.54 mol) of 2,2-dimethoxypropane (Aldrich), 40 ml of dry methanol, and 0.4 g of *p*-toluenesulfonic acid monohydrate was warmed gently on a steam bath for 1.5 hr with external stirring under a reflux condenser. To the dark red, homogeneous solution was added an additional 79.5 g (0.764 mol) of 2,2-dimethoxypropane and 450 ml of cyclohexane. The resulting two-layer solution was refluxed with internal stirring while the acetone–cyclohexane (observed bp 53.0°) and the methanol–cyclohexane (observed bp 54.5°) azeotropes were slowly removed at the head of a vacuum-jacketed, helix-packed distillation column. After 47 hr 590 ml of distillate had been collected and the vapor temperature was 79°. (Addition of 5 g of 2,2-dimethoxypropane followed by 15 min of total reflux lowered the vapor temperature to below 40° probably owing to the formation of isopropenyl methyl ether.) Anhydrous potassium carbonate (1 g) was added to neutralize the catalyst. The solvent and unreacted 2,2-dimethoxypropane were removed under reduced pressure and 148.3 g (nearly quantitative yield) of a light yellow liquid, bp 82–90° (0.02 mm), was collected, $[\alpha]^{20}$D° −49.4° (neat liquid) (lit.[13b] −53.1°). This material contained about 3% impurity by pmr spectroscopy. The vpc retention time (column A) corresponded to that observed for **8** contained in the mixture of ester–ketal homologs obtained from diethyl tartrate.

2,3-*O*-Isopropylidene-$\mathrm{L_g}$-threitol (9).—Yields of 64–87% of **9** were prepared according to the method of Feit[14] using the mixture of ester–ketal homologs prepared above. In most runs ethyl acetate was not used before the alkaline work-up procedure of Mićović and Mihailović[20] was employed.

1,4-Ditosyl-2,3-*O*-isopropylidene-$\mathrm{L_g}$-threitol (10).—This compound was prepared by the method of Rubin, *et al.*,[15] on a larger scale. The use of *p*-toluenesulfonyl chloride recrystallized from *n*-hexane and freshly distilled pyridine removed all fluctuation[15] in the yield. In a typical preparation, 55.1 g of **9** in 375 ml of pyridine yielded 142.9 g (90%) of **10**, mp 90.5–92 (lit.[15] 91–92°), after recrystallization from 400 ml of absolute ethanol. The specific rotation, $[\alpha]^{22}$D −12.4° (*c* 8.8 in $CHCl_3$), agreed with that reported.[15] The product was found to crystallize in two polymorphic forms:[21] fibrous needles from cold absolute ethanol, mp 80.8–82.0°, and compact crystals on slow crystallization from warm ethanol, mp 91.7–92.7°. The lower melting form was observed to change into the higher melting one during a 4-day period in cold ethanol to which both forms were added.

***S,S*-Diacetyl-2,3-*O*-isopropylidene-1,4-dithio-$\mathrm{L_g}$-threitol (11).**—A mixture of 46.7 g (0.10 mol) of the ditosylate (**10**), 25.7 g (0.225 mol) of potassium thiolacetate, and 250 ml of absolute ethanol was refluxed under dry nitrogen with internal stirring for 6 hr. The cooled mixture was filtered and the filtrate was washed with diethyl ether to give 41.2 g (97%) of potassium tosylate. The

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[13] (a) Y. Tsuzuki, *Bull. Chem. Soc. Jap.*, **10**, 255 (1935); (b) Y. Tsuzuki, *ibid.*, **11**, 362 (1936).

[14] P. W. Feit, *J. Med. Chem.*, **7**, 14 (1964).

[15] L. J. Rubin, H. A. Lardy, and H. O L. Fischer, *J. Amer. Chem. Soc.*, **74**, 425 (1952).

[16] Although the tosylate groups in **10** are primary, SN2 attack is somewhat hindered by the *gem*-dimethyl substitution on the five-membered ring. Thus conditions more vigorous than usual are often required for clean-cut replacement of the tosylate groups, *cf.* the conditions used for the reaction o **10** with sodium iodide in acetone.[15]

[17] E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co. Inc., New York, N. Y., 1958, p 30.

[18] (a) A. Lüttringhaus, S. Kabuss, W. Maier, and H. Friebolin, *Z. Naturforsch.*, **166**, 761 (1961); (b) A. Lüttringhaus, S. Kabuss, H. Prinzbach, and F. Langenbucher, *Ann.*, **653**, 195 (1962).

[19] Prepared in 88% yield by azeotropic esterification with benzene as the azeotropic component.

[20] V. M. Mićovoć and M. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

[21] Feit[14] observed similar polymorphs for the 1,4-dimesylate analogous to **10**.

ethanol solution was concentrated, diluted with diethyl ether, and filtered. The solution was again concentrated, diluted, and filtered. The ether was removed and the remaining liquid was distilled under reduced pressure, bp 101–115° (0.03 mm), to yield 24.8 g of a yellow liquid. Another sample prepared similarly was stripped of some low-boiling contaminants by vacuum distillation in a spinning-band apparatus, and an analytical sample was separated from two lower boiling impurities by vpc using column C: $[\alpha]^{22}\text{D} = -39.3°$ (c 3.1 in $CHCl_3$); $\nu_{\max}^{\text{neat}}$ 5.91 μ (C=O); $\tau_{\text{TMS}}^{CCl_4}$ 6.1–6.4 (multiplet, 2 H, CH), 6.8–7.0 (multiplet, 4 H, $-CH_2-$), 7.67 (singlet, 6 H, $-COCH_3$), 8.69 (singlet, 6 H, $C(CH_3)_2$).

Anal. Calcd for $C_{11}H_{18}O_4S_2$: C, 47.46; H, 6.52; S, 23.04. Found: C, 48.11; H, 6.60; S, 22.58.

2,3-*O*-Isopropylidene-1,4-dithio-L_g-threitol (12).—To a solution of 14 mg of sodium in 40 ml of dry methanol was added 24.7 g of **11**. Methanol and methyl acetate vapors (bp 54–56°) were slowly removed through an 8-cm Vigreux column during 8 hr. The reaction was followed by the disappearance of the infrared carbonyl absorption (5.91 μ) of **11**. An additional 15 ml of methanol containing 16 mg of dissolved sodium was added and the distillation was continued for 4 hr. Removal of the remaining solvent and direct distillation of the liquid residue yielded 17.3 g (quantitative yield) of colorless liquid: bp 60° (0.15 mm); $[\alpha]^{23°}\text{D}$ −13.0° (c 3.2 in $CHCl_3$); $\nu_{\max}^{\text{neat}}$ 3.87 (S–H), 7.39 and 7.44 μ (doublet, $C(CH_3)_2$); $\tau_{\text{TMS}}^{\text{neat}}$ 5.95–6.17 (multiplet, 2 H, CH), 7.08–7.37 (multiplet, 4 H, $-CH_2-$), 8.25 (triplet, J = 8 cps, 2 H, –SH), 8.64 (singlet, 6 *H*, $C(CH_3)_2$). Injection of 10 μl or larger samples into the vpc instrument resulted in some thermal decomposition to a hydroxylic material with both columns A and B.

(4*R*,5*R*)(+)-4,5-Isopropylidenedioxy-1,2-dithiane (13).—Oxygen gas was bubbled for 30 hr through a solution of 2.97 g of **12** and 1.80 g of potassium hydroxide in 50 ml of methanol and 20 ml of water. Some crystalline solid precipitated during this period. Addition of 40 ml of water and chilling overnight in the refrigerator caused the separation of 2.14 g (72%) of the cyclic disulfide ketal (**13**), mp 69.4–70.2° after drying in a desiccator with Drierite for 48 hr. Another sample, mp 69.4–70.8°, twice sublimed onto a cold finger under 0.05 mm at room temperature, showed the following properties: $[\alpha]^{22°}\text{D}$ +237° (c 2.3 in $CHCl_3$); $\lambda_{\max}^{\text{isooctane}}$ 287 mμ (ϵ 335) and 238 mμ (ϵ 179).

Anal. Calcd for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29; S, 33.35. Found: C, 43.91; H, 6.17; S, 33.27.

(2*R*,3*R*)(−)-1,4-Dithiothreitol = (−)-1,4-Dithio-L_g-threitol (2).—A solution of 4.15 g of the ketal dithiol (**12**) in 60 ml of 0.1 *N* hydrochloric acid–methanol (1:1) was heated under reflux for 4 hr with stirring. The solution was then diluted with 50 ml of water and continuously extracted with ethyl ether for 7 hr. Concentration of the ether extracts under reduced pressure and distillation at 84–97° (0.03 mm) yielded 2.65 g (80%) of product which slowly crystallized to a colorless, waxy solid.

Compound **2** was also prepared by hydrolysis of **11** in refluxing 2 *N* hydrochloric acid–methanol (2:1) for 1.5 hr under nitrogen. Neutralization of most of the acid, continuous extraction, and distillation as above gave comparable yields of liquid product, much of which solidified on seeding. Three sublimations of this latter material at 41° (0.02 mm) gave crystals which softened at 43° and melted at 45.0–47.0°; $[\alpha]^{22°}\text{D}$ −11.7 (c 2.4 in $CHCl_3$). Two recrystallizations from ethyl ether yielded needles, mp 48.2–49-8°.

Anal. Calcd for $C_4H_{10}O_2S_2$: C, 31.14; H, 6.54; S, 41.57. Found: C, 31.23; H, 6.67; S, 41.71.

(4*R*,5*R*)(+)-4,5-Dihydroxy-1,2-dithiane (3).—A mixture of 0.60 g of the dithiane ketal (**13**) in 35 ml of 0.1 *N* hydrochloric acid–methanol (4:3) become homogeneous after being stirred for 5 hr at room temperature. The resulting solution was extracted continuously with ethyl ether for 2 hr, after which the ether extracts were concentrated to dryness under reduced pressure. The crude product, mp 115–117°, was sublimed during 3 hr at 85° (0.01 mm), yielding 0.44 g (93%) of crystalline diol. Recrystallization from chloroform yielded a product melting at 116.2–117.8°: $[\alpha]^{23°}\text{D}$ +260 (c 0.32 in $CHCl_3$); $\lambda_{\max}^{H_2O}$ 281 mμ (ϵ 326) (the literature[2a] value for the racemic compound is $\lambda_{\max}^{H_2O}$ 283 mμ (α_m 273).

Anal. Calcd for $C_4H_8O_2S_2$: C, 31.57; H, 5.30; S, 42.14. Found: C, 31.63; 31.68; H, 4.80, 4.99; S, 42.20.

Registry No.—**2**, 16096-97-2; **3**, 16096-99-4; **11**, 16096-98-3; **12**, 16097-00-0; **13**, 16097-01-1.

Phenylmagnesium Bromide Induced S_N2' Reaction and Migrations of Fluorine in 1,1-Di(chlorodifluoromethyl)ethylene

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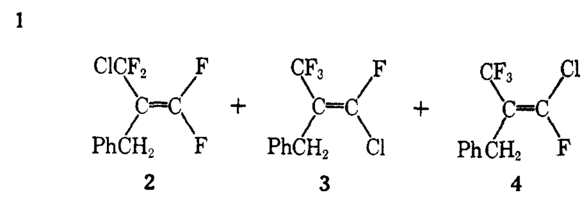
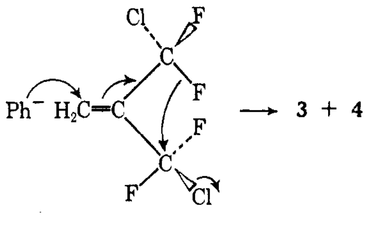
The S_N2' rearrangement[2] of highly fluorinated olefins of the type $H_2C{=}C(CF_2X)_2$ with lithium aluminum hydride or alkyl Grignard reagents has been previously reported as a general method for the preparation of terminal perfluoromethylene[3] olefins of the type $F_2C{=}C(CF_2X)R$, where X is F, Cl, or H and R is an alkyl group.

In this work 1,1-di(chlorodifluoromethyl)ethylene, **1**, was treated with phenylmagnesium bromide at approximately −20°. This led to a mixture of products from which the following compounds were isolated: 1,1-difluoro-2-chlorodifluoromethyl-3-phenylpropene, **2**, and the *cis* (**3**) and *trans* (**4**) isomers of 1-chloro-1-fluoro-2-trifluoromethyl-3-phenylpropene. An indication that the above reaction is more complicated than when alkyl Grignards or hydride ions are used as the nucleophilic species[3] is borne out by the presence of **3** and **4** whose combined yields were 25%, based on **1**. Other materials were also observed in the reaction mixture but they were not characterized because they were either present in small quantities or were intractable residues.



Formation of **2** can be easily rationalized with an S_N2' reaction.[4] Formation of **3** and **4** can be rationalized by a concerted nucleophilic attack on the $=CH_2$ group and an intramolecular substitution of chlorine by a fluorine atom to form the $-CF_3$ group. An inter-



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(1) Address all correspondence to the author at The Boeing Co., Seattle, Wash.

(2) R. E. Kepner, S. Winstein, and W. G. Young, *J. Amer. Chem. Soc.*, **71**, 115 (1949).

(3) M. H. Kaufman, J. D. Braun, and J. G. Shdo, *J. Org. Chem.*, **32**, 2749 (1967).

(4) Substitution of a chlorine atom by a fluorine atom has been previously observed in single substituted reactions of fluoride ions (in $CHCl_3$, CH_2Cl_2, and in acetone) with chlorine-containing olefins. See, for instance, W. T. Miller, J. H. Fried, and H. Goldwhite, *J. Amer. Chem. Soc.*, **82**, 3091 (1960).