2-propanol–ethyl acetate: nmr ($CDCl_3$) δ 1.2–1.9 (m, 6), 2.74 (s, 6), 2.5–3.0 (m, 3), 3.6 ($J$ = 2 Hz), 4.05 (d, 1, $J$ = 4 Hz), 7.29 (m, 4).

*Anal.* Calcd for $C_{14}H_{20}ClNO_2S$: C, 55.71; H, 6.68. Found: C, 55.31; H, 6.83. Molecular ion at $m/e$ 301.

**7-*p*-Chlorophenyl-6,7-epoxy-*N*,*N*-dimethylheptanesulfinamide (8c).**—The epoxide was prepared in 65% yield by the reaction of ylide **4c** and *p*-chlorobenzaldehyde. The oil was chromatographed on silica gel, developing with ethyl acetate. The infrared spectrum (neat) had peaks at 3050, 3920, 1490, 1450, 1175, 1065, 925, 828, and 778 $cm^{-1}$. The nmr ($CDCl_3$) had a multiplet at δ 7.28 (4 H, Ar **H**), a doublet at 4.03 ($J$ = 4 Hz), and a doublet ($J$ = 2 Hz) at 3.58 (combined area 1 H, Ar **CH** cis and trans), a three-proton multiplet at 3.1–2.6 (aliphatic –**CH** and $CH_2S$), a six-proton singlet at 2.73 [$N(CH_3)_2$], and at 1.8–1.1 [8 H, $-(CH_2)_4$] for the aliphatic chain.

*Anal.* Calcd for $C_{15}H_{22}ClNOS$: C, 57.04; H, 7.02. Found: C, 57.00; H, 7.24.

**Registry No.**—**3a**, 32846-71-2; **3b**, 32846-72-3; **3c**, 32846-73-4; **6**, 32846-69-8; **7**, 32846-70-1; **8a**, 32846-74-5; **8b**, 32846-75-6; *cis*-**8c**, 32846-76-7; *trans*-**8c**, 32958-92-2.

## A New Synthesis of 3,4-(Difluoromethylenedioxy)benzaldehyde[1]

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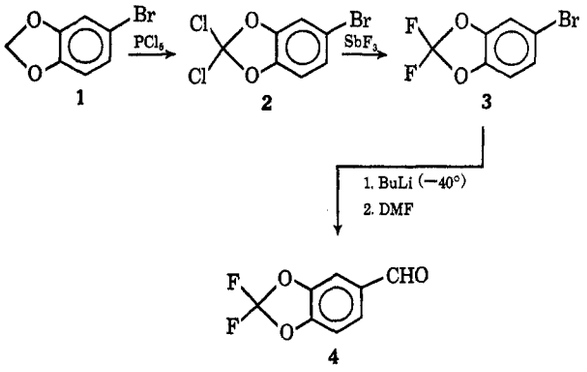
The methylenedioxyphenyl function is found in a broad spectrum of natural occurring materials[2] and appears to induce an enhancement or potentiation of biological activity.[3] The exchange of the methylene hydrogens for fluorine[4] represents an intriguing structural variation of biologically active substances containing this group. A particularly attractive intermediate for the introduction of this residue into organic molecules is 3,4-(difluoromethylenedioxy)benzaldehyde (**4**). Through a series of six synthetic steps Yagupol'skii[5] converted piperonylic acid into **4**, with an overall yield of approximately 30%. We wish to describe a much simpler three-step scheme to this valuable intermediate. The sequence of reactions is depicted below.

Chlorination of **1** with $PCl_5$ after the procedure of Barger[6] gave **2** in 83% yield. The exchange for fluorine was found to be very rapid and efficient if a solventless mixture of **2** and $SbF_3$ was heated under reduced pressure. In this manner, **3** distilled as it formed in a high state of purity. The chlorine–fluorine metathesis was considerably slower when the exchange was attempted in dioxane or hydrocarbon solvents.

Treatment of **3** with BuLi at −40° and subsequently adding freshly distilled dimethylformamide gave a 68% yield of **4**. An examination of the reaction products from this last step indicated that the halogen metal-interchange reaction occurred without loss of fluorine or rupture of the methylenedioxybenzene ring.[7]




In light of the ready formation of the aryllithium reagent from **3**, this reagent should also prove to be of value for the introduction of the 3,4-(difluoromethylenedioxy)phenyl functionality into organic substrates *via* the standard chemistry of organolithium reagents.

It is interesting to note that the alternative approach to **3**, *i.e.*, the exchange of methylene hydrogens for halogen prior to bromination, was ineffectual. Whereas the synthesis of (difluoromethylenedioxy)benzene was achieved without difficulty according to Yagupol'skii,[8] its bromination could not be realized without the destruction of the methylenedioxybenzene ring.

### Experimental Section

**3,4-(Dichloromethylenedioxy)bromobenzene (2).**—Phosphorus pentachloride (400 g) and 112 g of 3,4-(methylenedioxy)-bromobenzene[9] were heated at 80° for 3 hr. Distillation gave an 83% yield of **3**, bp 107–109° (4 mm), $n^{20}D$ 1.5770.

*Anal.* Calcd for $C_7H_3Cl_2BrO_2$: C, 31.23; H, 1.12; O, 11.90. Found: C, 31.44; H, 1.10; O, 12.04.

**3,4-(Difluoromethylenedioxy)bromobenzene (3).**—Compound **2** (50 g) was heated with 50 g of $SbF_3$ at 20 mm. Redistillation of the collected liquid gave 35.3 g (80% yield) of **3**, bp 78–79° (20 mm), $n^{20}D$ 1.4722.

*Anal.* Calcd for $C_7H_3F_2BrO_2$: C, 35.47; H, 1.28; Br, 33.76. Found: C, 35.80; H, 1.30; Br, 33.69.

**3,4-(Difluoromethylenedioxy)benzaldehyde (4).**—To a solution of **3** (36.5 g) in 150 ml of $Et_2O$ at −40° was added 100 ml of BuLi (1.6 *M*). After the addition was complete the reaction mixture was stirred for an additional hour at −40° and then treated with 33.6 g of DMF. The reaction was stirred for 1–2 hr at ambient temperature, treated with an exceess of $NH_4Cl$, and worked up in the usual manner. Vacuum distillation gave 19.6 g (68% yield) of **4**, bp 103–105° (20 mm).

**Registry No.**—**2**, 33070-31-4; **3**, 33070-32-5; **4**, 656-42-8.

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(2) D. A. Archer, *et al.*, *Proc. Chem. Soc.*, 168 (1963); A. R. Battersby, *ibid.*, 188 (1963); M. Sribney and S. Kirkwood, *Nature (London)*, **71**, 931 (1953).

(3) C. F. Wilkinson, *J. Agr. Food Chem.*, **15**, 139 (1967); R. L. Metcalf, *Annu. Rev. Entomol.*, **12**, 299 (1967); J. E. Casida, J. L. Engel, E. G. Essac, F. X. Kamienski, and S. Kuwatsuka, *Science*, **153**, 1130 (1966).

(4) The rationale for exchanging hydrogen for fluorine in biologically active materials has been related to (a) altered electronic effects, (b) greater chemical stability, and (c) similarity in steric requirements. Discussions of these points are detailed by M. B. Chenweth and L. P. McCarty, *Pharmacol. Rev.*, **15**, 673 (1963); W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, pp 454–463.

(5) L. M. Yagupol'skii and V. I. Troitskaya, *Zh. Obshch. Khim.*, **30**, 3129 (1960).

(6) G. Barger, *J. Chem. Soc.*, **93**, 566 (1908).

(7) Dichloromethylenedioxybenzene is reported to react with a variety of nucleophiles, including organometallics, to yield a product of displacement: H. Gross and J. Rusche, *Chem. Ber.*, **99** (8), 2625 (1966); H. Gross, *Chem. Abstr.*, **62**, 409a (1965).

(8) L. M. Yagupol'skii and V. I. Troitskaya, *Zh. Obshch. Khim.*, **34** (1), 307 (1964).

(9) Supplier: Frinton Laboratories, South Vineland, N. J.