Table V. Sample Data for the Rate Constant Calculated by Eq 7 for $SnCl_2$ Reduction of Nitrobenzene in 90% (v/v) EtOH at 30 °C [a]

t, s	$a-x$, M	x, M	$3b-x$, M	$10^2k'$, [b] M^{-1} s^{-1}
0	0.1455	0.0000	0.1500	
900	0.1353	0.0102	0.1398	0.1674
1800	0.1266	0.0189	0.1311	0.1655
3600	0.1120	0.0335	0.1165	0.1655
5400	0.1000	0.0455	0.1045	0.1673
7200	0.0911	0.0544	0.0956	0.1644
9000	0.0829	0.0626	0.0874	0.1660
10800	0.0762	0.0693	0.0807	0.1662

[a] Initial concentrations: $[SnCl_2] = a = 0.1455$ M, $[PhNO_2] = b = 0.05$ M, $[HCl]_{st} = 1.4512$ M.

relation coefficient (R) and standard deviation (S) show that the meta E_σ is more appropriate than Taft's ortho E_σ for these reactions. Apparently, these results show that ortho substituents exert polar effects similar to those of meta substituents because of the steric inhibition of resonance.

Experimental Section

Materials. The inorganic and organic reagents used were all of commercial guaranteed grade and used without further purification. A 90% or 55% (v/v) ethanol solution of HCl was prepared by mixing 35% aqueous HCl or HCl gas with the appropriate amount of 99% ethanol and water, and the concentration was confirmed by alkalimetry.

Kinetics. A 90% or 55% (v/v) ethanolic solution (25 mL) containing an appropriate amount of HCl and nitro compounds (2.5 mmol) and another HCl (same amount) acidic 90% or 55% (v/v) ethanolic solution (25 mL) containing $SnCl_2$ (7.5 mmol) were placed in a thermostated bath to reach a constant temperature (30 °C). The two solutions were mixed to start the reaction, and aliquots were pipetted out at appropriate intervals of time. The concentration of $SnCl_2$ in the aliquot was determined by iodometry. For the estimation of the HCl concentration, an initial aliquot was introduced to aqueous sodium citrate and titrated with 0.5 N NaOH with phenolphthalein as an indicator to subtract the amount of HCl produced by the hydrolysis of $SnCl_2$.

The HCl-catalyzed $SnCl_2$ reduction of nitro compounds ($ArNO_2$) obeys the stoichiometric equation (eq 6).[4]

$$ArNO_2 + 3SnCl_2 + 7HCl \rightarrow ArNH_2{\cdot}HCl + 3SnCl_4 + 2H_2O \quad (6)$$

Assuming that initial concentration of $SnCl_2$ is a and that of $ArNO_2$ is b and that the consumed concentration of $SnCl_2$ at time t is x,, we can express $[ArNO_2]$ at time t as $b - x/3$ on the basis of eq 6. Hence

$$v = -d[SnCl_2]/dt = dx/dt = k'(a-x)(b-x/3)$$

or

$$k' = \frac{6.909}{t(3b-a)} \log \frac{a(3b-x)}{3b(a-x)} \quad (7)$$

A typical calculation of rate data for nitrobenzene is shown in Table V as an example.

Registry No. Nitrobenzene, 98-95-3; 2-nitrophenol, 88-75-5; 1-methyl-2-nitrobenzene, 88-72-2; 1-methoxy-2-nitrobenzene, 91-23-6; 2-nitro-1,1'-biphenyl, 86-00-0; 2-nitrobenzoic acid, 552-16-9; 1-fluoro-2-nitrobenzene, 1493-27-2; 1-iodo-2-nitrobenzene, 609-73-4; 1-chloro-2-nitrobenzene, 88-73-3; 1-bromo-2-nitrobenzene, 577-19-5; 1-methyl-3-nitrobenzene, 99-08-1; 1-methyl-4-nitrobenzene, 99-99-0; 2-nitrobenzonitrile, 612-24-8; 1-(2-nitrophenyl)ethanone, 577-59-3; 1-ethyl-2-nitrobenzene, 612-22-6; 1,3-dimethyl-2-nitrobenzene, 81-20-9; stannous chloride, 7772-99-8; ethanol, 64-17-5; 1-ethoxy-2-nitrobenzene, 610-67-3; 1,2-dinitrobenzene, 528-29-0.

Selectively Deuterated and Optically Active Cyclic Ethers

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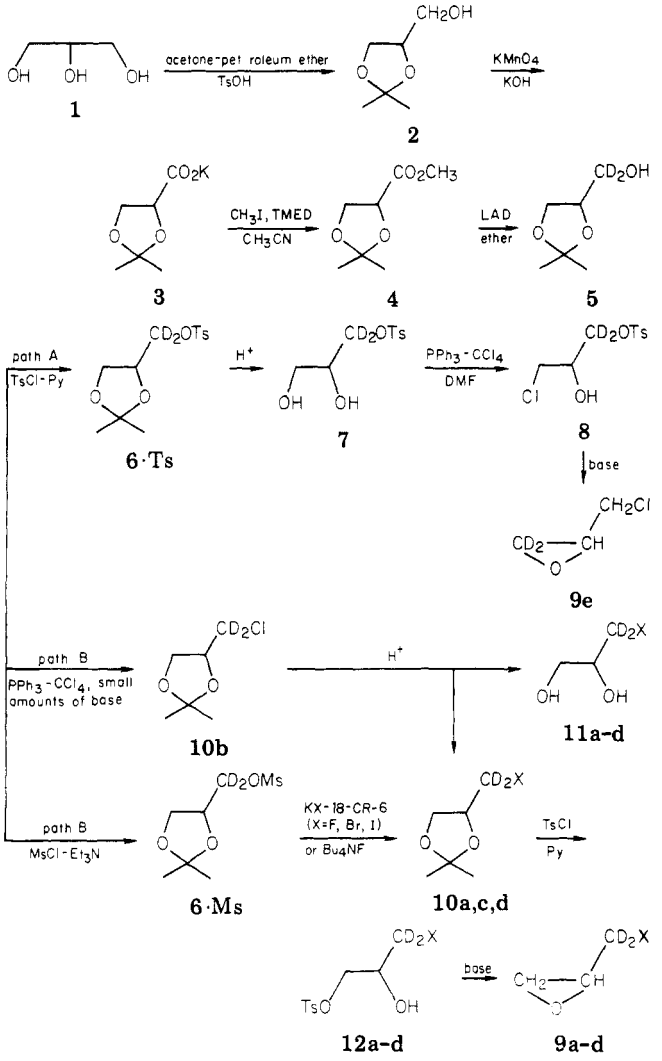
The high versatility and importance of optically active or selectively deuterated compounds in synthetic and mechanistic organic chemistry are well-known. We have been interested in optically active cyclic ethers, particularly the epihalohydrin type, as starting materials in the synthesis of various chiral compounds. The optically active epihalohydrins (Cl, Br, I) are versatile starting materials in synthesizing polyether-type phase-transfer catalysts (PTC), while their fluoro analogue can be transformed into a biologically interesting compound.[1-4] We reported in an earlier paper a mild and effective method for chlorine displacement in three- and four-membered cyclic ethers by potassium halide–18-crown-6 (KX–18-CR-6) systems, and, further, the reaction mechanisms of fluorination of epichlorohydrin and 3,3-bis(chloromethyl)oxetane were also elucidated, using their selectively deuterated derivatives.[5] In this paper, we report the synthesis of selectively deuterated epihalohydrins (F, Cl, Br, I) and 3,3-bis(chloromethyl)-d_2)oxetane and some of our observations on the stereochemistry of each transformation. Further, the synthesis of optically active epihalohydrins, especially the optically active epifluorohydrin, from (*S*)-glycerol 1,2-acetonide ((*S*)-**2**), using mainly KX–18-CR-6 (X = F, Br, I), is reported. To our knowledge, this is the first report on the synthesis of optically active epifluorohydrin. The direct halogenation of the presynthesized optically active epichlorohydrin with the same reagents gave the racemized products.[5] The selectively deuterated or optically active compounds reported herein are expected to find a variety of uses in organic chemistry.

The synthetic schemes are relatively straightforward. Baldwin reported the synthesis of (*R*)- and (*S*)-epichlorohydrins ((*R*)-**18b**, (*S*)-**18b**) from (*S*)-**2**.[6] However, the yield of (*S*)-**18b** is variable and, moreover, dependent on reaction conditions. Since the stereochemistry of each transformation is clearly defined, we thought that the selectively deuterated epichlorohydrins (**9b**, **9e**) could be synthesized from selectively deuterated glycerol-*3,3-*d_2 1,2-acetonide (**5**). **5** was synthesized by the lithium aluminum deuteride (LAD) reduction of methyl glycerate 2,3-acetonide (**4**) and further transformed into selectively deuterated **9e** according to the Scheme I. The alteration of the order of the tosylation and chlorination steps was also attempted in order to improve the yield of the epichlorohydrin (path B). Selectively deuterated epihalohydrins other than epichlorohydrin (X = F, Br, I) were synthesized by our method through the mesylate (path C). Monodeuterated (*S*)-glycerol 1,2-acetonide and several of

(1) Changas, G. S.; Fondy, T. P. *Biochemistry* **1971**, *10*, 3204.
(2) Eisenthal, R.; Harrison, R.; Lloyd, W. J.; Taylor, N. F. *Biochem. J.* **1972**, *130*, 199.
(3) Fondy, T. P.; Pero, R. W.; Karker, K. L.; Changas, G. S.; Batzold, F. H. *J. Med. Chem.* **1974**, *17*, 697.
(4) Eager, R. G., Jr.; Bachovchin, W. W.; Richards, J. H. *Biochemistry* **1975**, *14*, 5523.
(5) Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* **1980**, *45*, 3930.
(6) Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876.

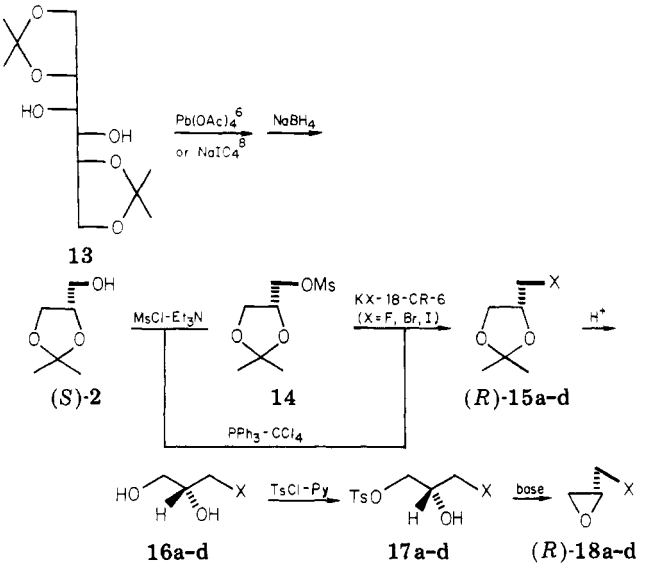
0022-3263/82/1947-3581$01.25/0

Scheme I. Synthetic Routes to Selectively Deuterated Epihalohydrins[a]



[a] Throughout this paper a-d, Ms, and Ts indicate the fluoro, chloro, bromo, iodo, methanesulfonyl, and *p*-toluenesulfonyl derivatives, respectively.

Scheme II. Routes to (*R*)-Epihalohydrins



the fluorinated compounds used as intermediates in our deuterated and optically active series have already been reported.[1,4,24]

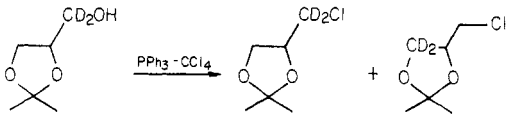
Optically active epihalohydrins were synthesized according to Scheme II.

The oxidation of **2** to potassium glycerate 2,3-acetonide (**3**) is smooth; however, incomplete oxidation gives 3-methoxy-1,2-propanediol acetonide as a side product, along with the main product **4**, after treatment with CH_3I. The reduction of **4** by LAD afforded the selectively deuterated alcohol **5** in a reasonable yield. Baldwin synthesized (*S*)-**18b** from (*S*)-**2** by the reaction path corresponding to path A in Scheme I.[6] The yield in the chlorination of 3-(tosyloxy)-1,2-propanediol, and subsequently that of (*S*)-**18b**, is very much dependent on the reaction conditions and the order of adding the reagents, and the use of dry dimethylformamide (DMF) and/or CCl_4 seems to be essential for good yield. The same is also true in the synthesis of 1-chloro-2,3-epoxypropane-*3,3-d*$_2$ (**9e**) from 3-(tosyloxy)-1,2-propane-*3,3-d*$_2$-diol (**7**). Either sodium ethylene glycolate (Na·EG) in ethylene glycol (EG) or $Ca(OH)_2$ in H_2O can be used as base for the ring-closure reaction. Na·EG may be a better choice because of the ease of the separation of the product. The yield of (*S*)-**18b** or **9e** by path A according to the reported method[6] is generally poor, ranging only 2–10% from the glycerol acetonide with P_2O_5-dried CCl_4, but the stereochemistry is well-defined as shown in Scheme I. The isotopic purity of **9e** is 98%, almost the same as that of LAD.

Since **9e** could be obtained irrespective of the base used in the ring-closure step, the reason for the low yield of **9e** or (*S*)-**18b** from **7** or its nondeuterated derivative seemed to lie in the chlorination step. Firstly, the improvement of chlorination procedure seemed necessary. Selective chlorination at primary OH group, e.g., of **7**, is essential for the good yield of **9e**. However, reagents other than triphenylphosphine (PPh_3)–CCl_4, such as $SOCl_2$–pyridine (Py), PCl_3–Py, or $POCl_3$–Py gave only poor results. Thorough drying of **7** and CCl_4 and DMF are critical to achieve reasonable yields. We could considerably improve the yield to 40% by adding CCl_4 to a dry DMF solution of 3-(tosyloxy)-1,2-propanediol and PPh_3.

Secondly, the order of chlorination and tosylation steps was altered (path B). **2** has been reported to be chlorinated in 80% yield with PPh_3–CCl_4.[9] If the stereochemistry of 3-chloro-1,2-propane-*3,3-d*$_2$-diol acetonide (**10b**) could be well-defined, reaction path B might be advantageously used for the synthesis of **9b** or (*R*)-**18b**.

The chlorination of **5**, by the reported method,[9] afforded a 55:45 mixture of **10b** and 3-chloro-1,2-propane-*1,1-d*$_2$-diol acetonide (**10e**), determined by ^1H NMR (see the spectral differences in the Experimental Section), as shown in eq 1.



5 **10b** **10e** 55:45 (1)

Such deuterium scrambling between side chain and ring was observed under several sets of ordinary anhydrous chlorination conditions. The ratios of 56:44, 47:53; 49:51; and 52:48 were observed with PPh_3–CCl_4–DMF, $POCl_3$, PCl_3, and $[(CH_3)_2NCH{=}CHCl]^+Cl^-$,[10] respectively. Ap-

(7) McClure, D. E.; Engelhardt, E. L.; Mensler, K.; King, S.; Saari, W. S.; Huff, J. R.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 1826.
(8) Eibl, H. *Chem. Phys. Lipids* **1981**, *28*, 1.
(9) Lee, J. B.; Nolan, T. J. *Can. J. Chem.* **1966**, *44*, 1331.

Table I. Synthesis of 3,3-Bis(chloromethyl-d_2)oxetane from 2,2-Bis(chloromethyl-d_2)-1,3-propanediol (17)[a]

no.	esterification agent	temp, °C	time, h	% yield of esterification[b]	% yield of oxetane[c]
1	TsCl	20[d]	20	70	84
2	TsCl	20[e]	20	73	79
3	TsCl	70[e]	20	100	62
4	MsCl	20[f]	20	100	73
5	MsCl	20	20	100	83
6	MsCl	70[g]	20	67	19
7	BroCl	20[h]	20	100	92
8	BroCl	80[h]	5	90	80
9	TFAA	20[i]	20	52	trace
10	TFAA	80[i]	5	52	trace

[a] 1.77 g (10 mmol) of **17** was reacted at specified temperature with 10 mmol of the esterification agent, and the resulting monoester was treated with NaH (0.4 g, 60% in oil) as shown in the Experimental Section. [b] Yield after evaporating off the solvent. [c] Determined by gas chromatography. [d] TsCl was added in small portions during 30 min at 10 °C. [e] TsCl was added in small portions during 30 min at 20 °C. [f] MsCl was added during 30 min at 0 °C. [g] MsCl was added during 30 min at 30 °C. [h] BroCl was added in small portions during 30 min at 50 °C. [i] TFAA was added during 30 min at 80 °C.

parently, opening and reclosure of the ring have occurred before chlorination. This scrambling seemed to be caused by small amounts of water (H_2O) and the acid liberated in the chlorination step.[6,11] Small amounts of a tertiary amine were reported to be effective to prevent such an interconversion.[11] The use of anhydrous solvents and reagents and small amounts of a tertiary amine greatly enhanced the selectivity of **10b** over **10e**. The use of a nonnucleophilic base was particularly effective, and reproducible yields and stereochemistry could be obtained. The selectivity was greatly improved from 55:45 to 88:12, 85:15, and 88:12 with 3 mol % of Py, triethylamine (Et_3N), and *N,N*-diisopropylethylamine (DIE), respectively. However, the yield declined to 10–30% with Py or Et_3N. DIE gave a reasonable yield. Drying the solvent with P_2O_5 was not very effective in improving the selectivity. Calcium hydride (CaH_2) dried CCl_4 gave reasonable yields with high selectivity. While a ratio of 91:9 could be reached even without an amine, improved and excellent selectivities of 95:5, 98:2, and 96:4 were achieved by the use of 75 mol % of 2,6-di-*tert*-butylpyridine (51% yield), 1,8-diazabicyclo-[5.4.0]undec-7-ene (43%), and DIE (50%), respectively. These facts clearly stress that rigorously anhydrous conditions are very crucial for the high selectivity of **10b**.

Since the isotopic purity of LAD is 98%, the fact that 98% of deuterium is contained in the side chain in **10b** implies that the chlorination proceeds with the retention of stereochemistry at C-2 of **10b**. Tosylation was smooth, and selectively deuterated **9b** was obtained in good yields (40–60%) from **5** after the treatment with a base. When above transformations (path B) are applied to (*S*)-**2**, practically optically pure (*R*)-3-chloro-1,2-propanediol acetonide ((*R*)-**15b**) can be expected to be obtained, and, in fact, (*R*)-**18b** of high optical purity was obtained in good yield through subsequent transformations shown in Scheme II. If halogens other than chlorine were introduced in (*R*)-**15** ((*R*)-**15a,c,d**), optically active (*R*)-epihalohydrins ((*R*)-**18a,c,d**) should be similarly obtainable. Direct iodination[12] of (*S*)-**2** or iodination through the tosylate[13] of (*S*)-**2** by reported methods gave respectively the racemized and highly optically active iodides. In place of the tosylate we have used the distillable mesylate. Halogenation of (*R*)-**14** by our method[5] (KX–18-CR-6, X = F, Br, I) afforded the halides (*R*)-**15a,c,d** in moderate to good yields. Here, we stress the necessity of starting from highly optically pure (*S*)-**2** to get highly optically active (*R*)-**18** compounds.

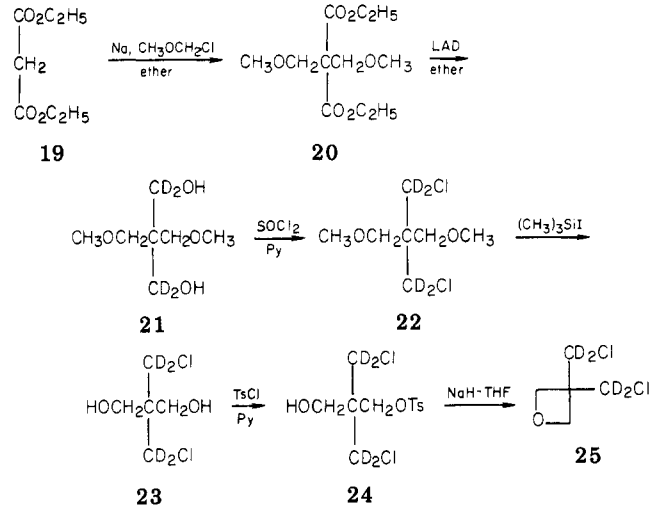
Although many methods have been reported on the synthesis of (*S*)-**2** from D-mannitol (**13**)[6,8,11,14-19] or L-serine,[20] the optical purity of the product (*S*)-**2** is dependent on the method. Among several methods we have tried, the ones in ref 6, 8, and 19 gave reproducible yields and high optical purity of the product.

The yields and optical rotation data of **18a–d** are as follows. **18a**: 53% yield, bp 86 °C, $[\alpha]^{16}_D$ −6.1° (2.12, MeOH) (the chiral purity determined in the presence of tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium [Eu(tfc)$_3$] at the concentration of 2.0 mol % was 97 ± 3%). **18b**: 70% yield, bp 118 °C, $[\alpha]^{15}_D$ −32.8° (1.74, MeOH). **18c**: 50% yield, bp 138 °C, $[\alpha]^{19}_D$ −15.6° (4.10, EtOH). **18d**: 34% yield, bp 167 °C, $[\alpha]^{15}_D$ −9.7° (1.5, MeOH). The optical rotation data are those obtained by our procedures and do not necessarily mean those of optically pure compounds. The ^{1}H NMR spectra are in good accordance with the reported ones.

3,3-Bis(chloromethyl-d_2)oxetane (**25**) was synthesized according to Scheme III. The synthesis of diethyl bis(methoxymethyl)malonate (**20**) from diethyl malonate (**19**) was achieved in a single step in reasonable yield.[21] [**Caution**: Chloromethyl methyl ether is a cancer suspect agent. Handle in hood with gloves.] Deuterium atoms were introduced selectively by the reduction of the two ester groups with LAD, giving 4,4-bis(hydroxymethyl-d_2)-2,6-dioxaheptane (**21**). Chlorination followed by a subsequent slow ether cleavage with trimethylsilyl iodide[22] gave the desired 2,2-bis(chloromethyl-d_2)-1,3-propanediol (**23**) in good yield. The diol **23** was converted to the monoester by treatment with TsCl, MsCl, *p*-bromobenzenesulfonyl chloride (BroCl), or trifluoroacetic anhydride (TFAA). Finally, 3,3-bis(chloromethyl-d_2)oxetane (**25**) was obtained by treating the resulting crude monoester with a base. The results of the oxetane synthesis are shown in Table I.

(10) Hepburn, D. R.; Hudson, H. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 754.
(11) Becu, C.; Anteunis, M. *J. Fluorine Chem.* **1975**, *5*, 381.
(12) Bevan, T. H.; Malkin, T.; Smith, D. B. *J. Chem. Soc.* **1955**, 1383.
(13) Baer, E.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1948**, *70*, 609.
(14) Baer, E.; Fischer, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463.
(15) Baer, E. *Biochem. Prep.* **1952**, *2*, 31.
(16) LeCocq, J.; Ballon, C. E. *Biochemistry* **1964**, *3*, 976.
(17) Bird, P. R.; Chadha, J. S. *Tetrahedron Lett.* **1966**, 4541.
(18) Kohan, G. K.; Just, G. *Synthesis* **1974**, 192.
(19) Schmidt, U.; Talbiersky, J.; Bartkowiak, F.; Wild, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 198.
(20) Lok, C. M.; Ward, J. P. *Angew Chem., Int. Ed. Engl.* **1976**, *16*, 115.
(21) Hill, A. J.; Keach, D. T. *J. Am. Chem. Soc.* **1928**, *48*, 257.
(22) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

Scheme III. Synthesis of Selectively Deuterated 3,3-Bis(chloromethyl)oxetane



Experimental Section

Glycerol 1,2-Acetonide (2): 2 was prepared in 98% yield from glycerol (1; 15.0 g, 1.63 mol) and acetone (400 mL) in petroleum ether (400 mL) in the presence of TsOH (1.0 g).[23]

Potassium Glycerate 2,3-Acetonide (3). 2 (58.7 g, 0.44 mol) in H_2O (200 mL) containing KOH (26.8 g, 0.48 mol) was oxidized with (about 50%) excess aqueous $KMnO_4$ solution at 0–10 °C until the color of permanganate ion remained for 30 min. Excess permanganate was decomposed with MeOH, and the filtrate was evaporated to dryness. The residue was suspended in EtOH (200 mL) and again evaporated to dryness to remove the remaining H_2O as much as possible. This residue was used without further purification.

Methyl Glycerate 2,3-Acetonide (4). A suspension of 3 from above in MeCN (500 mL) was reacted with MeI (85.2 g, 0.60 mol) in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMED; 5 g, 0.04 mol) at 50 °C for 5 h with vigorous stirring. After the formed salt was filtered off, the filtrate was distilled under reduced pressure to give pure 4 as a colorless liquid (45.8 g, 65% based on 2): bp 88 °C (28 mm); ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 4.00–4.80 (ABC type m, 3 H, CH_2CH). Anal. Calcd for $C_7H_{12}O_4$: C, 52.47; H, 7.56. Found: C, 52.44; H, 7.55. The incomplete oxidation of 2 to 3 gave 3-methoxy-1,2-propanediol acetonide as a side product along with the main product 4, bp 72 °C (28 mm). Small amounts of the side product could be removed by washing the crude oil in ether with water by taking the advantage of the higher solubility of the side product in water. A Vigreux column (30 cm long) was used to separate the products. ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.42 (s, 3 H, OCH_3), 3.50–4.80 (m, 5 H, CH_2CHCH_2).

Glycerol-*3,3*-d_2 1,2-Acetonide (5). To an ice-cooled solution of 4 (32.0 g, 0.20 mol) in Et_2O (150 mL) was added LAD (4.2 g, 0.10 mol) as a suspension in Et_2O (100 mL) in 1 h. After being refluxed for 3 h, the reaction mixture was diluted with Et_2O (200 mL), decomposed with H_2O (7.2 g, 0.40 mol), centrifuged if necessary, and filtered. The solid material was washed thoroughly with Et_2O and then Soxhlet-extracted with EtOH (100 mL) for 3 h. The filtrate and extract were combined, concentrated, and distilled under reduced pressure to give pure 5 (20.0 g, 75%): bp 88.5 °C (28 mm); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 3.38 (s, 1 H, OH), 3.65–4.33 (ABC type m, 3 H, CH_2CH). Similar procedures were also reported.[4]

3-(Tosyloxy)-1,2-propane-*3,3*-d_2-diol Acetonide (6·Ts): was obtained in 90% yield from 5 (23.0 g, 0.17 mol) according to the method of Baldwin:[6] mp 48.5–48.9 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 6 H, $(CH_3)_2C$), 2.47 (s, 3 H, $CH_3C_6H_4$), 3.65–4.50 (ABC type m, 3 H, CH_2CH), 7.40 and 7.87 (2 d, 4 H, C_6H_4, J = 9.5 Hz).

3-(Tosyloxy)-1,2-propane-*3,3*-d_2-diol (7). Hydrolysis of 6·Ts, also according to Baldwin, gave 7 quantitatively, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3 H, CH_3), 3.45–3.67, 3.80–4.10 (2 m, 5 H, $HOCH_2CHOH$), 7.40, 7.87 (2 d, 4 H, C_6H_4, J = 9.5 Hz).

1-Chloro-2,3-epoxypropane-*3,3*-d_2 (9e). CCl_4 (60 mL) was added to 7 from above and PPh_3 (39.6 g, 0.15 mol) in DMF (200 mL). An exothermic reaction occurred. After 15 min, stirring was resumed and continued for 3 h at ambient temperature. The resulting mixture was worked up similarly to Baldwin's procedure.[6] The formed crude 9e was collected under vacuum into a dry ice–acetone trap (quoted as "trapped" hereafter). Redistillation gave pure 9e (5.6 g, 40%): ^{1}H NMR ($CDCl_3$) δ 3.25 (dd, 1 H, CH, J_1 = 7.8 Hz, J_2 = 8.0 Hz), 3.60 (pseudo d, 2 H, CH_2, J = 7.9 Hz). Mixing PPh_3 and CCl_4 initially according to Baldwin usually resulted in poor yield (2–10%).

3-Chloro-1,2-propane-*3,3*-d_2-diol Acetonide (10b). 5 (15.2 g, 0.10 mol) was dissolved in 50 mL of Na-dried benzene (Bz) together with PPh_3 (27.5 g, 0.105 mol) and a tertiary amine[11] (0.2–50 mmol), and the mixture was added dropwise during 30 min to refluxing CaH_2-dried CCl_4 (50 mL) containing the same amine (0.1–25 mmol). The reaction mixture was then cooled to room temperature, and the crude products were "trapped" and fractionally distilled, giving 13.3 g of 10b (78%): bp 52 °C (12 mm); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.68–4.46 (ABC type m, 3 H, CH_2CH). The reaction in the absence of an amine were done in a similar manner to give a mixture of 10b and 10e. 10e: ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.34–4.12 (ABC type m, 3 H, CH_2CH). The absorptions at δ 3.34–4.46 were used to determine the ratio of 10b to 10e.

3-(Mesyloxyy)-1,2-propane-*3,3*-d_2-diol Acetonide (6·Ms). To an ice-cooled solution of 5 (13.6 g, 0.10 mol) in Et_3N (12.1 g, 0.12 mol) and toluene (Tol; 100 mL) was added MsCl (13.6 g, 0.12 mol) in Tol (40 mL) during 1 h with stirring. The crude products, which were worked up similarly to 6·Ts, were fractionally distilled to give 18.6 g of the product (86%): bp 128 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.03 (s, 3 H, CH_3SO_3), 3.63–4.46 (ABC type m, 3 H, CH_2CH).

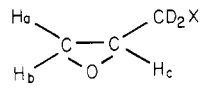
3-Halogeno-1,2-propane-*3,3*-d_2-diol Acetonide (10a,c,d). 6·Ms (6.3 g, 3.0 mmol) was reacted with KX (X = F, Br, I) in the presence of appropriate amounts of 18-CR-6 in a suitable solvent at a designated temperature for 48 h. The crude products were "trapped" and purified by fractional distillation. 10a (X = F; (bp 124 °C; KF = 150 mmol, 18-CR-6 = 7.5 mmol; triglyme 30 mL, 140 °C, 40%): ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.65–4.65 (ABC type m with FCCH coupling at methine, 3 H, CH_2CH). 10c (X = Br; bp 63 °C (13 mm)): KBr = 60 mmol, 18-CR-6 = 1.5 mmol; MeCN 30 mL, reflux, 80%): ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 3.70–4.48 (ABC type m, 3 H, CH_2CH). 10d (X = I; bp 50 °C (7 mm)); KI = 110 mmol, 18-CR-6 = 1.5 mmol; MeCN 30 mL, reflux, 70%): ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 3.60–4.44 (ABC type m, 3 H, CH_2CH). Equimolar amounts of Bu_4NF from Fluka to 6·Ms (2.1 g, 1.0 mmol) in THF (10 mL) under reflux gave an excellent yield of 10a (80%) in 5 h.

3-Halogeno-1,2-propane-*3,3*-d_2-diol (11a–d). Compounds 10b–d were hydrolyzed with 1 N HCl similarly to the method used for 6·Ts. The products were extracted with EtOAc and isolated by fractional distillation. 10a was hydrolyzed with ethanolic H_2SO_4.[2] 11a (X = F; bp 73 °C (3 mm)): ^{1}H NMR (CD_3OD) δ 3.50–3.85 (ABC type m, 3 H, CH_2CH). 11b (X = Cl; bp 95 °C (7 mm)): ^{1}H NMR (CD_3OD) δ 3.60–4.10 (ABC type m, 3 H, CH_2CH). 11c (X = Br; bp 102 °C (7 mm)): ^{1}H NMR (CD_3OD) δ 3.56, 3.62, 3.66, 3.68, 3.80–4.20 (ABC type m, 3 H, CH_2CH). 11d (X = I; mp 46–48 °C): ^{1}H NMR (CD_3OD) δ 3.67 (br s, 3 H, CH_2CH).

3-Halogeno-1-(tosyloxy)-2-propan-3,3-d_2-ol (12a–d). Compounds 11a–d were transformed into tosylates by treatment with TsCl similar to the procedure used for 5. The crude products were used directly for the further reaction.

3-Halogeno-1,2-epoxypropane-*3,3*-d_2 (9a–d). Compounds 12a–d were treated with Na·EG similarly to the procedure used for the preparation of 9e to give 9a–d. Satisfactory yields were obtained respectively with 12a (68%), 12b (62%), 12c (60%), and 12d (55%). 9a: ^{1}H NMR ($CDCl_3$) δ 2.60–3.10 (ABC type m, AB

(23) Penoll, M.; Newman, M. S. "Organic Syntheses", Collect Vol. III; Wiley: New York, 1955; p 502.
(24) Lloyd, W. J.; Harrison, R. *Carbohydr. Res.* **1971**, *20*, 133.



part, 2 H, CH_2), 3.11–3.66 (ABC type m, C part with FCCH coupling, 1 H, $CHCD_2F$). **9b**: ^1H NMR ($CDCl_3$) δ 2.65 (dd, 1 H, H_b, J_1 = 5.0 Hz, J_2 = 2.6 Hz), 2.84 (dd, 1 H, H_a, J_1 = 5.0 Hz, J_2 = 4.0 Hz), 3.25 (dd, 1 H, $CHCD_2Cl$, J_1 = 4.0 Hz, J_2 = 2.6 Hz). **9c** (X = Br) ^1H NMR ($CDCl_3$) δ 2.69 (dd, 1 H, H_b, J_1 = 5.0 Hz, J_2 = 2.1 Hz), 2.97 (dd, 1 H, H_a, J_1 = 5.0 Hz, J_2 = 4.0 Hz), 3.30 (dd, 1 H, $CHCD_2Br$, J_1 = 4.0 Hz, J_2 = 2.1 Hz). **9d** (X = I) ^1H NMR ($CDCl_3$) δ 2.63 (dd, 1 H, H_b, J_1 = 5.0 Hz, J_2 = 1.9 Hz, 3.00 (dd, 1 H, H_a, J_1 = 4.0 Hz, J_2 = 5.0 Hz), 3.37 (dd, 1 H, $CHCD_2I$, J_1 = 4.0 Hz, J_2 = 1.9 Hz).

(*S*)-Glycerol 1,2-Acetonide ((*S*)-2). This compound was synthesized by the reported procedures[6,8,19] from D-mannitol: $[\alpha]^{25}_D$ +11.7° (6.42, MeOH).

(*R*)-3-(Mesyloxy)-1,2-propanediol Acetonide (14) and (*R*)-3-Halogeno-1,2-propanediol Acetonide (15a–d). (*S*)-2 was transformed into **14**, **15a,c,d**, and **15b** similarly to the procedure used for **6**-Ms, **10a,c,d**, and **10b**, respectively. **14**: 88% yield; bp 127 °C (0.22 mm); $[\alpha]^{27}_D$ −3.43° (6.42, Bz); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 3.03 (s, 3 H, CH_3SO_3), 3.63–4.66 (overlapped 2 ABC type m, 5 H, CH_2CHCH_2). **15a**: 40% yield by KF, 80% by Bu_4NF; bp 124 °C; $[\alpha]^{16}_D$ +12.7° (2.44, Bz); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.65–4.65 (ABC type m with FCCH coupling at methine, 3 H, CH_2CH), 4.49 (q, 2 H, CH_2F, J_{FCH} = 46.8 Hz, J_{HCCH} = 4.8 Hz). **15b**: 80% yield; bp 63 °C (37 mm); $[\alpha]^{25}_D$ +35.9° (5.03, Bz); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_2), 3.35–3.62 (ABC type BC part q, 2 H, CH_2Cl), 3.66–4.45 (ABC type m with complicated pattern at methine, 3 H, $CHCH_2CH_2Cl$). **15c**: 70% yield; bp 63 °C (15 mm); $[\alpha]^{25}_D$ +36.4° (5.80, Bz); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 3.30–3.47 (ABC type BC part q, 2 H, CH_2Br), 3.68–4.57 (ABC type m with complicated pattern at methine CH_2CHCH_2Br). **15d**: 75% yield; bp 50 °C (7 mm); $[\alpha]^{26}_D$ +34.5 (5.94, Bz); ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.15–3.33 (ABB′ type BB′ q, 2 H, CH_2I), 3.66–4.56 (ABC type m with complicated pattern at methine, 3 H, CH_2CHCH_2I).

(*R*)-3-Halogeno-1,2-propanediol (16a–d) and (*R*)-3-Halogeno-1,2-epoxypropane (18a–d). Compounds **15a–d** were converted to **18a–d** through **16a–d** and **17a–d** similarly to the conversion through **11a–d** and **12a–d**. **16a**: 60% yield; 73 °C (2.8 mm); $[\alpha]^{11}_D$ −17.4° (3.05, EtOH); ^1H NMR (CD_3OD) δ 3.00–3.90 (ABC type m, 3 H, CH_2CH), 4.35 (q, 2 H, CH_2F, J_{JCH} = 48.0 Hz, J_{HCCH} = 5.6 Hz). **16b**: 86% yield; bp 95 °C (7 mm); $[\alpha]^{26}_D$ +3.85° (5.56, $CHCl_3$); ^1H NMR (CD_3OD) δ 3.50–4.17 (overlapped 2 ABC type m, 5 H, CH_2CHCH_2). **16c**: 80% yield; bp 102 °C (7 mm); $[\alpha]^{25}_D$ −3.94° (5.07, $CHCl_3$); ^1H NMR (CD_3OD) δ 3.42, 3.52 (ABC type ($J/_{\Delta\nu} \simeq 0.1$) 2 broad s, 2 H, $BrCH_2$), 3.66, 3.72, 3.76, 3.78 (ABC type ($J/_{\Delta\nu} \simeq 0.2$) q, 2 H, OCH_2), 3.65–4.35 (m, 1 H, CH). **16d**: 80% yield; mp 46–48 °C; $[\alpha]^{23}_D$ −4.2° (5.10, EtOH); ^1H NMR (CD_3OD) δ 3.25 (d, 2 H, CH_2I, J = 4.5 Hz), 3.67 (br s, 3 H, $CHCH_2$).

Diethyl Bis(methoxymethyl)malonate (20).[21] To small pieces of Na wire (11.5 g, 0.50 mol) in Et_2O (1 L) was added diethyl malonate (**19**; 40 g, 0.25 mol) dropwise with vigorous stirring, and the mixture was allowed to react until all the Na was consumed (about 5 h). To this reaction mixture was added chloromethyl methyl ether (40.25 g, 0.50 mol) [**caution**: chloromethyl methyl ether is a cancer suspect agent; handle in a hood; all the apparatus should be washed with aqueous alkaline to decompose the remaining agent] dropwise with stirring with ice cooling. The reaction mixture was then refluxed for 10 h and set aside overnight. The formed salt was filtered off and washed with ether (200 mL). After the removal of the solvent, fractional distillation under reduced pressure gave 30 g of the product with a boiling range of 81–100 °C (3 mm). Redistillation gave pure **20** (25.1 g, 40%), bp 85–86 °C (3.5 mm).

4,4-Bis(hydroxymethyl-d_2)-2,6-dioxaheptane (21). **20** (24.8 g, 0.10 mol) in Et_2O (50 mL) was reduced similarly to the procedure used for **5** with LAD (4.2 g, 0.10 mol) in Et_2O (300 mL). The crude **21** was proved to be sufficiently pure by gas chromatography and NMR analyses and was used for the following synthesis without further purification: 15.2 g (90%) yield; ^1H NMR ($CDCl_3$) δ 3.26 (br s, 2 H, OH), 3.37 (s, 6 H, CH_3), 3.45 (s, 4 H, CH_2). Corresponding nondeuterated compound absorbs at δ 3.24 (br s, 2 H, OH), 3.37 (s, 6 H, CH_3), 3.45 (s, 4 H, CH_2), 3.70 (s, 4 H, CH_2OH).

4,4-Bis(chloromethyl-d_2)-2,6-dioxaheptane (22). To an ice-cooled solution of **21** (15.2 g, 0.09 mol) in Py (15.9 g, 0.20 mol) was added dropwise $SOCl_2$ (23.8 g, 0.20 mol). The reaction mixture was gradually heated to 100 °C in 4 h, maintained for 2 h at 100 °C, diluted with CH_2Cl_2 (100 mL) after cooling to room temperature, and washed with 1 H HCl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic solution was dried (Na_2SO_4), concentrated, and distilled under reduced pressure to give **22** (16.1 g) as a colorless liquid: 89% yield; bp 78.5 °C (10 mm); ^1H NMR ($CDCl_3$) δ 3.37 (s, 6 H, CH_3), 3.42 (s, 4 H, CH_2). Nondeuterated compound absorbs at δ 3.37 (s, 6 H, CH_3), 3.42 (s, 4 H, CH_2), 3.60 (s, 4 H, CH_2Cl). Anal. Calcd for $C_7H_{10}D_4Cl_2O_2$: C, 40.99; H, 4.91, D, 3.92; Cl, 34.63. Found: C, 40.91; H + D, 8.93; Cl, 34.57.

2,2-Bis(chloromethyl-d_2)-1,3-propanediol (23). **22** (16.1 g, 0.080 mol) was heated with Me_3SiI (36.0 g, 0.18 mol) at 100 °C for 5 days in dry chlorobenzene (50 mL) in a reaction tube sealed under vacuum. The contents were poured into 2 N methanolic HCl (200 mL), and the mixture was refluxed for 2 h. The volatile components were removed at reduced pressure, and the residue was purified by sublimation, after treatment with sodium thiosulfate, if necessary, in order to remove liberated I_2 (94%): mp 79.0–80.0 °C; ^1H NMR (CD_3OD) δ 3.61 (s, 4 H, CH_2OH). Anal. Calcd for $C_5H_6D_4Cl_2O_2$: C, 33.92; H, 3.42; D, 4.55; Cl, 40.05. Found: C, 34.10; H + D, 8.10; Cl, 39.96. Nondeuterated **17**: ^1H NMR (CD_3OD) δ 3.63 (s, 4 H, CH_2OH), 3.67 (s, 4 H, CH_2Cl); mp 76.0–76.2 °C.

2,2-Bis(chloromethyl-d_2)-3-(tosyloxy)propanol (24). To a solution of **23** (14.2 g, 0.080 mol) in Py (60 mL) was added portionwise TsCl (15.1 g, 0.080 mol) with efficient stirring during 30 min at 20 °C. After being stirred for 30 min, the reaction mixture was maintained for 20 h at room temperature, diluted with CH_2Cl_2 (100 mL), and washed with 2 N HCl until the aqueous washings became acidic. The H_2O layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and finally evacuated at 0.2 mm for 18 h at 25 °C. The resulting material was used without further purification. **23** was similarly converted to the mesylate and *p*-bromobenzenesulfonate by treating with MsCl or BroCl, respectively, in Py. **23** was also treated with an equimolar amount of TFAA. The mixture was used in the subsequent reaction after evaporating off the volatile material at ambient temperature (0.2 mm).

3,3-Bis(chloromethyl-d_2)oxetane (25). The crude tosylate above was dissolved in THF (100 mL), and NaH (3.2 g, 60% in oil) was added at 0 °C in small portions. After the addition, the reaction system was refluxed for 1 h, and the salt that formed was filtered off after cooling. The filtrate was concentrated and fractionally distilled to yield 4.69 g of **25**: 85.2% yield; bp 81.5–81.7 °C (10 mm); ^1H NMR ($CDCl_3$) δ 4.47 (s, 4 H, OCH_2). Anal. Calcd for $C_5H_4D_4Cl_2O$: C, 37.76; H, 2.54; D, 5.07; Cl, 44.58. Found: C, 37.68; H + D, 7.74; Cl, 44.33.

Cyclization of *N*-(2-Biphenylyl)hydroxylamine Derivatives to N-Substituted Carbazoles[1]

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The cyclization of *N*-(2-biphenylyl)hydroxylamine (**1a**) to carbazole (**2a**) has been the subject of many reports.[3-7]

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