SELECTIVE CLEAVAGE OF UNSYMMETRICAL 2,2-SPIRO-1,3-DIOXOLANES I KETALIZATION OF 5-BROMO-3-METHOXYCARBONYL-4,5,6,7-TETRAHYDRO-BENZO[b]FURAN-4-ONE AND ITS ANALOGS

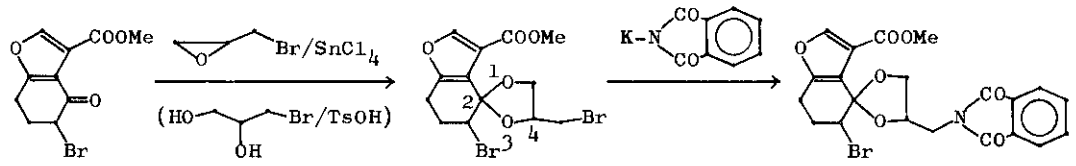
Makiko Sakai
Research Laboratories, Shionogi & Co., Ltd.
Sagisu 5-12-4, Fukushimaku, Osaka 553, Japan

Abstract Reaction of 2-bromocyclohexanones fused with an aromatic or heteroaromatic ring (1-4) with epibromohydrin or 3-bromo-1,2-propanediol gave two (a and b) or four (a, b, c, and d) isomers of the corresponding 2,2-spiro-4-bromomethyl-1,3-dioxolanes 5-8, respectively. The stereochemistry of the reactions is discussed.

The stereochemistry of 1,3-dioxolane has recently received much attention. Yandovskii and Temnikova[1] reported that the reaction of benzaldehyde with p-substituted β,β-dimethylstyrene oxide in the presence of stannic chloride gave a mixture of cis and trans isomers of 4,4-dimethyl-2-phenyl-5-(p-substituted phenyl)-1,3-dioxolanes. Tishchenko et al[2] reported that the reaction of methyl thiocyanate in dichloromethane with epichlorohydrin in the presence of boron trifluoride afforded 5-chloromethyl-2-methylthio-2-oxazoline in 62 % yield. This paper deals with the reaction of 2-bromocyclohexanone fused with an aromatic or heteroaromatic ring (1-4) with dl-epibromohydrin, dl-3-bromo-1,2-propanediol, or glycerol in the presence of stannic chloride or p-toluenesulfonic acid, and discusses the stereochemistry of the products.

dl-5-Bromo-3-methoxycarbonyl-4,5,6,7-tetrahydrobenzo[b]furan-4-one 1[5] (3.2 mM) in 1,2-dichloroethane (4 ml) was ketalized with dl-epibromohydrin (6.4 mM) in the presence of stannic chloride (0.32 mM) at 26-28°C for 2 h and gave a mixture of stereoisomeric 2,2-spiro-4-bromomethyl-1,3-dioxolanes 5 (5'-bromo-4-bromomethyl-6',7'-dihydro-3'-methoxycarbonyl-spiro[1,3-dioxolane-2,4'-(5'H)-benzo-[b]furans]), which was fractionated by column chromatography into two crystalline compounds, 5a and 5b, in 16 and 18 % yields, respectively (Scheme 1). On the other hand, azeotropic distillation of 1 (1.5 mM) in petroleum ether (20 ml) with

Scheme 1



1 5-a,b (5-a,b,c,d) 10-a,b,c, or d

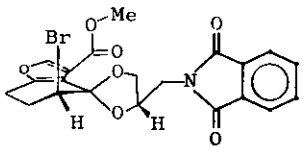
Table 1 Preparation and Modification of Dioxolanes

Starting material	Reagent (Conditions)	Dioxolane	Yield (%) a	b	c	d	Total yield (%)
1[5]	Epibromohydrin/$SnCl_4$ (in $(CH_2Cl)_2$, rt/2 h)	5[9]	16	18	–	–	34
1	Bromopropanediol/TsOH (in petr.ether, reflux/17 h)	5	5	10	6	11	32
2[6]	Epibromohydrin/$SnCl_4$ (in CH_2Cl_2, rt/2.5 h)	6	46	47	–	–	93
2	Bromopropanediol/TsOH (in benzene, reflux/5.5 h)	6	20	27	18	28	93
3[7]	Epibromohydrin/$SnCl_4$ (in $(CH_2Cl)_2$, rt/2 h)	7	41	45	–	–	86
4[8]	Epibromohydrin/$SnCl_4$ (in $(CH_2Cl)_2$, rt/24 h)	8	27	29	–	–	56
4	Bromopropanediol/TsOH (in benzene, reflux/2 d)	8	20	28	24	27	99
2[6]	Glycerol/TsOH (in benzene, reflux/7 d)	9[10]	15	18	15	20	68
9c[10]	TsCl/Py (rt/3.5 h)	11c[12]	–	–	85	–	85
6a,b	1-$PrNH_2$ (reflux/4 d)	12a,b[13]	43	44	–	–	87
11c[12]	" (reflux/5 d)	12c[12]	–	–	89	–	89
7a,b	" (reflux/6 d)	13a,b[14]	42	45	–	–	87
8	" (reflux/5 d)	14[15]	18	25	21	24	88
12a,c[13]	BsCl/Et_3N (rt/24 h)	15a,c[16]	45	–	41	–	86
14a,b,c	" (rt/5 h)	16a,b,c[17]	26	36	31	–	93

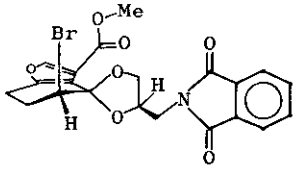
dl-3-bromo-1,2-propanediol (15 mM) in the presence of p-toluenesulfonic acid (0.05 mM) for 17 h gave 5a (5 %) and 5b (10 %) together with two other crystalline compounds, 5c (6 %) and 5d (11 %)[9] (Table 1). These four compounds were found to

be stereoisomers of the possible configurations of the bromine atom at position 5', the unsymmetrical 1,3-dioxolane ring, and the bromomethyl group at position 4, according to elemental analysis data and ir, nmr, and mass spectra[9]. An isomerization of the compounds 5a in dichloromethane (reflux 24 h) in the presence of anhydrous p-toluenesulfonic acid (0.033 M equiv.) gave the isomer 5d (37 %) with recovery of 5a (59 %) by neutralization with triethylamine, while another isomerization of 5b afforded 5c (25 %) with recovery of 5b (71 %) under the same conditions. The structures of 5a and 5b were conclusively determined by X-ray analysis using the corresponding phthalimide derivatives, 10a and 10b[11], as depicted in Scheme 2[4]. In 10a, the bonds of C(5')-Br and C(2)-O(3) are trans and the phthalimidomethyl group at position 4 has an endo configuration (endo means a configuration near the furan plane), while in 10b, those of C(5')-Br and C(2)-O(3) are also trans and the phthalimidomethyl group at position 4 has an exo configuration. Accordingly, the structures of two other phthalimidomethyl compounds, 10c and 10d[11], are considered to be cis-endo and cis-exo configurations, respectively (Scheme 2).

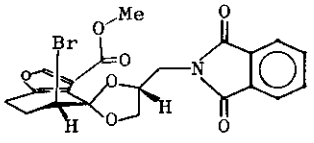
Scheme 2



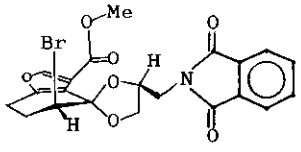
10a: trans-endo



10b: trans-exo



10c: cis-endo



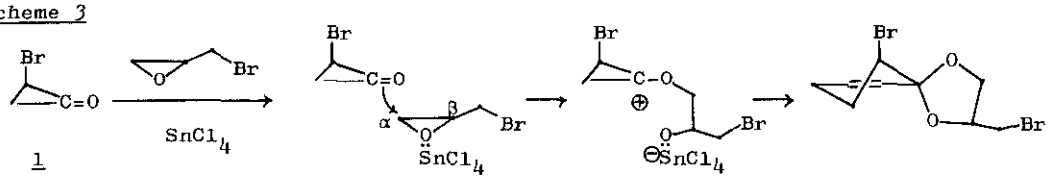
10d: cis-exo

It is known that the epoxide ring of epichlorohydrin is opened at the α-carbon by the attack of a nucleophile in the presence of boron trifluoride[2] or of an acid with or without a base[3]. Activation of dl-epibromohydrin with stannic chloride would result in a δ+ charge distribution mainly at the epoxide's α-carbon. The carbonyl oxygen of 1 could approach the α-carbon charged with δ+ in the least hindered direction (Phase A, Scheme 3). In the following Phase B, the attraction

between the carbenium ion (C ⊕) and the complex-anion (O:$SnCl_4$⊖) would afford those final products, trans-dioxolanes 5a and 5b (Phase C). On the other hand, in the ketalization of the furanone 1 with dl-3-bromo-1,2-propanediol, four possible stereoisomers of 1,3-dioxolanes (5a, 5b, 5c, and 5d) were isolated by column chromatography. This result seems reasonable since the ketalization could run first with a predominant attack by the primary alcoholic hydroxy group to the carbonyl carbon followed by cyclization with water elimination.

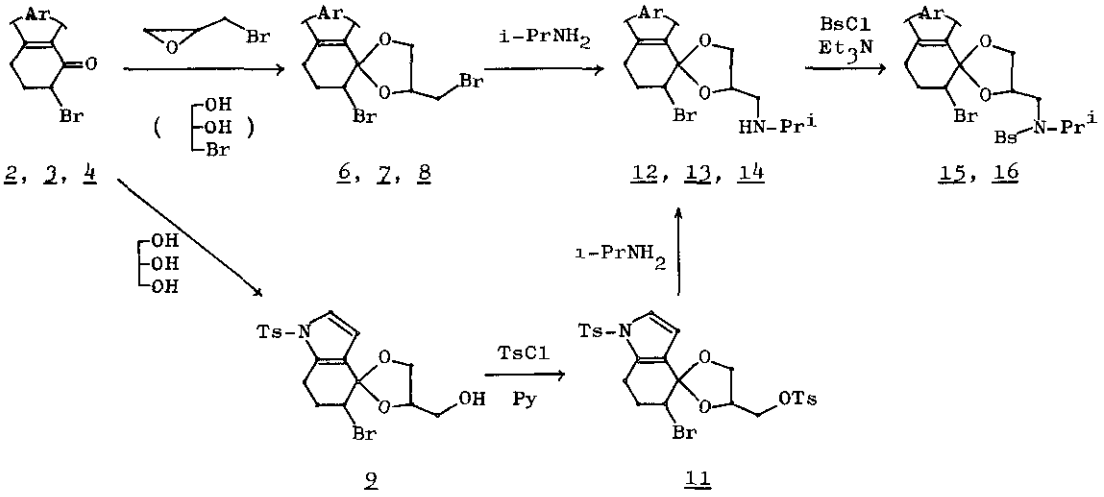
Similar results were obtained with the ketalization and modification of 5-bromo-1-p-toluenesulfonyl-4,5,6,7-tetrahydroindol-4-one 2[6], 5-bromo-4,5,6,7-tetrahydrobenzo[b]thiophen-4-one 3[7], and 2-bromo-1,2,3,4-tetrahydronaphthalen-1-one 4[8] with dl-epibromohydrin, dl-3-bromo-1,2-propanediol, or glycerol and gave the corresponding 2,2-spiro-4-(substituted methyl)-1,3-dioxolanes 6-9 (Scheme 4 and Table 1).

Scheme 3



1 A B C (5a and 5b)

Scheme 4



2, 3, 4 6, 7, 8 12, 13, 14 15, 16

9 11

Ar : 2, 6, 12, 15 = Ts-N ; 3, 7, 13 = S ; 4, 8, 14, 16 =

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5. The furanone 1 was prepared from 4-oxo-4,5,6,7-tetrahydrobenzo[b]furan-3-carboxylic acid (H. Stetter and R. Lauterbach, Ann. Chem., 1962, 655, 20) by methylation (CH_2N_2, 96 % yield) followed by bromination ($PyHBr_3$, 45 %), mp 80-81°C (decomposition). ir ν_{max}^{KBr} cm^{-1}: 1705, 1688. ^{1}H-nmr ($CDCl_3$) δ (Hz): 2.52 (2H, ddd, J=8, 4.5, 4), 2.91 (dt, J=17.5, 8), 3.89 (s), 4.59 (1H, t, J=4), 7.99 (s).

6. The bromoindolone 2 (colorless crystals, mp 150-152°C) was prepared from 4,5,6,7-tetrahydroindol-4-one according to the method of W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, J. Org. Chem., 1971, 36, 1232.

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9.

Cpd	mp (°C)	ir	^{1}H-nmr ($CDCl_3$) δ (Hz)			ms m/z (M^+)
		ν_{max}^{KBr} cm^{-1}	-COOMe	C(4)-H	C(2')-H	
5a	123-4	1735	3.79(s)	4.54(dddd, J=6.5, 6.5, 6.5, 6.5)	7.86(s)	412, 410, 408
5b	112-3	1705	3.84(s)	4.82-5.20 (m)	7.96(s)	412, 410, 408
5c	93-4.5	1729	3.78(s)	4.85(dddd, J=7, 7, 7, 7)	7.84(s)	412, 410, 408
5d	102-3.5	1729	3.78(s)	4.87-5.23 (m)	7.83(s)	412, 410, 408

10.

Cpd	mp (°C)	ir ν_{max} cm^{-1}	^{1}H-nmr ($CDCl_3$) δ (Hz) p-Me	C(3')-H
9c	—	3580 ($CHCl_3$)	2.41 (s)	6.31 (1H, d, J=3.5)
9d	139-40	3530 (KBr)	2.42 (s)	6.31 (1H, d, J=3)

11.

Cpd	mp (°C)	ir ν_{max}^{KBr} cm^{-1}	^{1}H-nmr ($CDCl_3$) δ (Hz) -COOMe	C(4)-H	ms m/z (M^+)
10a	133.5-4.5	1712, 1732 (sh)	3.73 (s)	4.51-4.92 (m)	477, 475
10b	139-140	1711 (br)	3.72 (s)	4.73-5.08 (m)	477, 475
10c	184-5	1714, 1742	3.79 (s)	4.60-5.04 (m)	477, 475
10d	154-5	1709, 1734 (sh)	3.73 (s)	4.90-5.23 (m)	477, 475

12.

Cpd	ir $\nu_{max}^{CHCl_3}$ cm^{-1}	^{1}H-nmr ($CDCl_3$) δ (Hz) p-Me	C(4)-H	C(3')-H
11c	1179, 1374	2.41 (s), 2.44 (s)	4.43-4.73 (m)	6.22 (d, J=3)
11d	1180, 1376	2.42 (s), 2.45 (s)	4.46-4.79 (m)	6.23 (d, J=3)

13.

Cpd	^{1}H-nmr ($CDCl_3$) δ (Hz) $-CHMe_2$	p-Me	1H of C(5)-H_2	C(3')-H
12a	1.07 (d, J=6.5)	2.43 (s)	3.93 (dd, J=7.5, 7.5)	6.31 (d, J=3)
12b	1.06 (d, J=6.5)	2.42 (s)	3.92 (dd, J=7.5, 7.5)	6.35 (d, J=3.5)
12c	1.07 (d, J=6.5)	2.43 (s)	3.91 (dd, J=7.5, 7.5)	6.32 (d, J=3)
12d	1.06 (d, J=6.5)	2.42 (s)	3.91 (dd, J=8, 8)	6.35 (d, J=3.5)

14.

Cpd	^{1}H-nmr ($CDCl_3$) δ (Hz) $-CHMe_2$	1H of C(5)-H_2	C(3')-H	C(2')-H
13a	1.06 (d, J=6.5)	4.01 (dd, J=7.5, 7.5)	7.04 (d, J=5.5)	7.17 (d, J=5.5)
13b	1.07 (d, J=6.5)	4.00 (dd, J=7.5, 7.5)	7.11 (d, J=5.5)	7.22 (d, J=5.5)

15. 14d: ^{1}H-nmr ($CDCl_3$) δ (Hz): 1.07 (d, J=6), 3.90 (1H, dd, J=7.5, 7.5), 4.30 (1H, dd, J=7.5, 7.5).

16.

Cpd	^{1}H-nmr ($CDCl_3$) δ (Hz)		
	-CH<u>Me</u>$_2$	p-<u>Me</u>	-C<u>H</u>$_2$-N<
<u>15a</u>	1.01(d, J=7), 1.12(d, J=7)	2.41(s)	3.24(dd, J=6, 15), 3.47(dd, J=5, 15)
<u>15c</u>	0.98(d, J=7), 1.14(d, J=7)	2.41(s)	3.26(dd, J=6, 15), 3.49(dd, J=5, 15)

17.

Cpd	mp (°C)	^{1}H-nmr ($CDCl_3$) δ (Hz)	
		-CH<u>Me</u>$_2$	-C<u>H</u>$_2$-N<
<u>16a</u>	168.5-9	1.02(d, J=6.5),1.14(d, J=6.5)	3.30(dd, J=6, 15),3.51(dd,J=4.5, 15)
<u>16b</u>	128-9	1.00(d, J=6.5),1.06(d, J=6.5)	3.23(dd, J=5.5, 15),3.46(dd,J=5, 15)
<u>16c</u>	151-2	1.03(d, J=7),1.17(d, J=7)	3.30(dd, J=6, 15), 3.54(dd,J=5.5, 15)
<u>16d</u>	—	1.02(d, J=6.5),1.14(d, J=6.5)	3.37(dd, J=6, 15),3.60(dd,J=5.5, 15)

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