[Chem. Pharm. Bull. 31(10)3418—3423(1983)]

Reaction of Epichlorohydrin with Hydroxybenzo[*b*]furan

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(Received January 27, 1983)

Epichlorohydrin [^{14}C-1,2] (**4**) was condensed with 2-acetyl-7-hydroxybenzo[*b*]furan potassium salt (**3**) to give two radiochemical regio-isomeric 2-acetyl-7-glycidyloxybenzo[*b*]furans (**5a** and **5b**). The ratio, **5a**/**5b**, was determined to be 5/7 by using ^{14}C-radioisotopic tracer techniques. The present results showed that the reaction proceeds through two different paths in which the phenolate (**3**) attacks at C-1 of **4** to give **5a** and at C-3 to give **5b**, the latter path being more favorable than the former.

Keywords——epichlorohydrin; nucleophilic substitution; 2-acetyl-7-glycidyloxybenzo-[*b*]furan; radiochemical regio-isomer; ^{14}C-radioisotopic tracer technique; cleavage of carbon chain; reaction mechanism

Epichlorohydrin has high chemical reactivities toward nucleophiles such as phenolate, thiophenolate, cyanate and carboxylate due to its epoxy group.[1-6] In particular, epichlorohydrin reacts with phenolates to provide phenyl glycidyl ethers.[4] In spite of considerable efforts to investigate the reaction mechanisms, two different mechanisms (path a and path b in Chart 1) have been proposed or presumed for several similar electrophilic reactions of epichlorohydrin.[7-10]

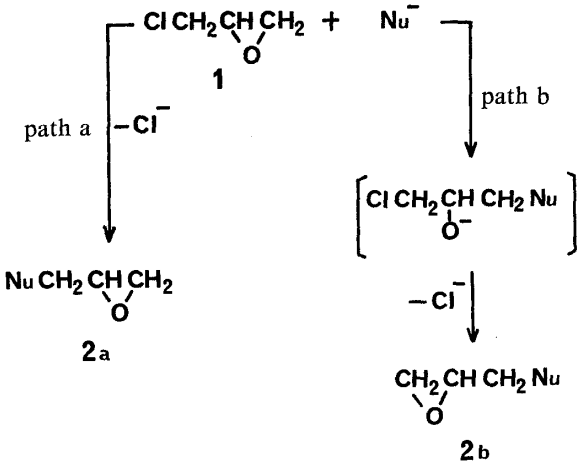

Chart 1

In this paper, we would like to describe the reaction mechanism in the reaction of epichlorohydrin with the phenolate (**3**) on the basis of radiochemical tracer techniques using epichlorohydrin [^{14}C-1,2] as a starting material.

Thus, the reaction between equimolar amounts of epichlorohydrin [^{14}C-1,2] (**4**) with a specific radioactivity of 11.41 mCi/mmol, in which ^{14}C should be distributed equally at C-1 and C-2,[11] and 2-acetyl-7-hydroxybenzo[*b*]furan potassium salt (**3**) in dimethylformamide

gave radioactive oxirane (**5a**+**5b**),[12] the specific radioactivity of which was 11.45 mCi/mmol. The oxirane (**5a**+**5b**) was treated with isopropylamine in ethanol to give radioactive 2-acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzo[*b*]furan (**6a**+**6b**),[13-15] which was purified by preparative thin-layer chromatography (TLC) on silica gel plates. The radiochemical purity of the resulting product was shown to be 98.0% by TLC and autoradiography (Chart 2).

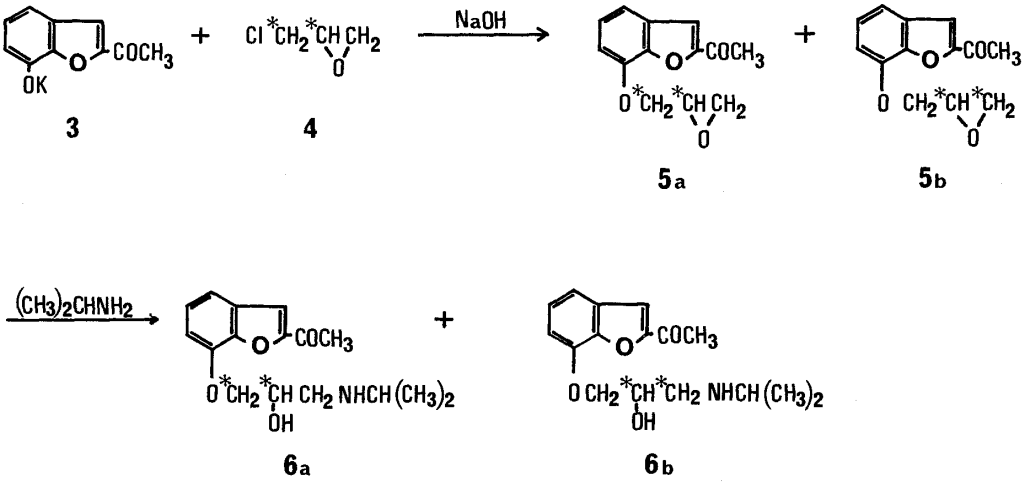

Chart 2

It could be assumed that the oxirane (**5a**+**5b**) and amine (**6a**+**6b**) were both mixtures of two radiochemical regio-isomers and we checked this assumption as follow. The oxirane (**5a**+**5b**) with a specific radioactivity of 2.545 μCi/mmol was easily hydrolyzed by treatment with 25% sulfuric acid in acetone for 1 h at room temperature to give 2-acetyl-7-(2,3-dihydroxypropoxy)benzo[*b*]furan (**7a**+**7b**) which was purified by column chromatography on silica gel to give colorless needles (specific radioactivity 2.427 μCi/mmol, recovery 95.4%).

Subsequently, oxidative cleavage of the side chain of the glycol (**7a**+**7b**) was performed.

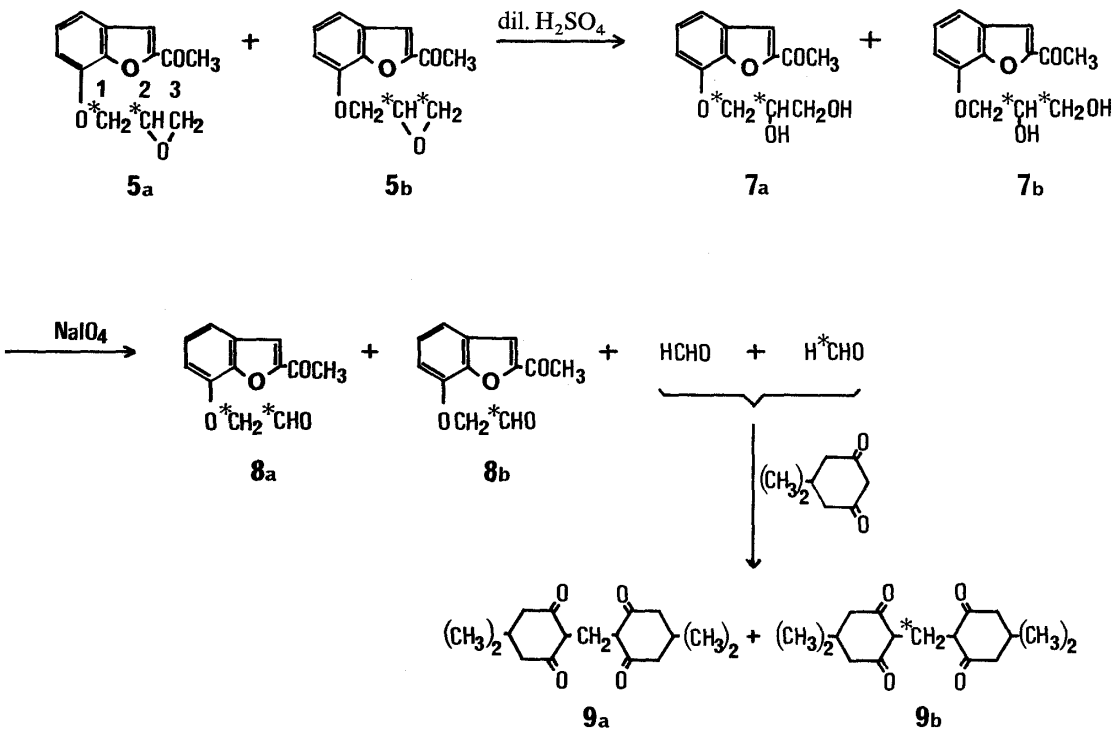

Chart 3

First, cleavage was carried out by oxidation of the glycol (**7a**+**7b**) (specific radioactivity 0.8472 μCi/mmol) with freshly prepared aqueous 12.5% sodium metaperiodate solution at 24 °C followed by cooling the reaction mixture to −20 °C to precipitate 2-acetyl-7-formylmethoxybenzo[*b*]furan (**8a**+**8b**) almost quantitatively, and then the filtrate, which contained formaldehyde and radioactive formaldehyde ($H^{14}CHO$), was treated with an excess of dimedone to afford methylenebisdimedone (**9a**+**9b**)[16,17] with a specific radioactivity of 0.2351 μCi/mmol (recovery 27.8%) (Chart 3).

Attempts to purify the aldehyde (**8a**+**8b**) were unsuccessful, so **8a**+**8b** was similarly treated with dimedone in acetone to give 2-acetyl-7-[{2,2-bis(5,5-dimethyl-1,3-dioxocyclohexan-2-yl)}ethoxy]benzo[*b*]furan (**10a**+**10b**).

Oxidation of **8a**+**8b** with silver oxide in aqueous sodium hydroxide solution gave 2-acetyl-7-carboxymethoxybenzo[*b*]furan (**11a**+**11b**), which could be purified by preparative TLC and subsequent recrystallizations (specific radioactivity 0.5773 μCi/mmol, recovery 68.1% based on **7a**+**7b**).

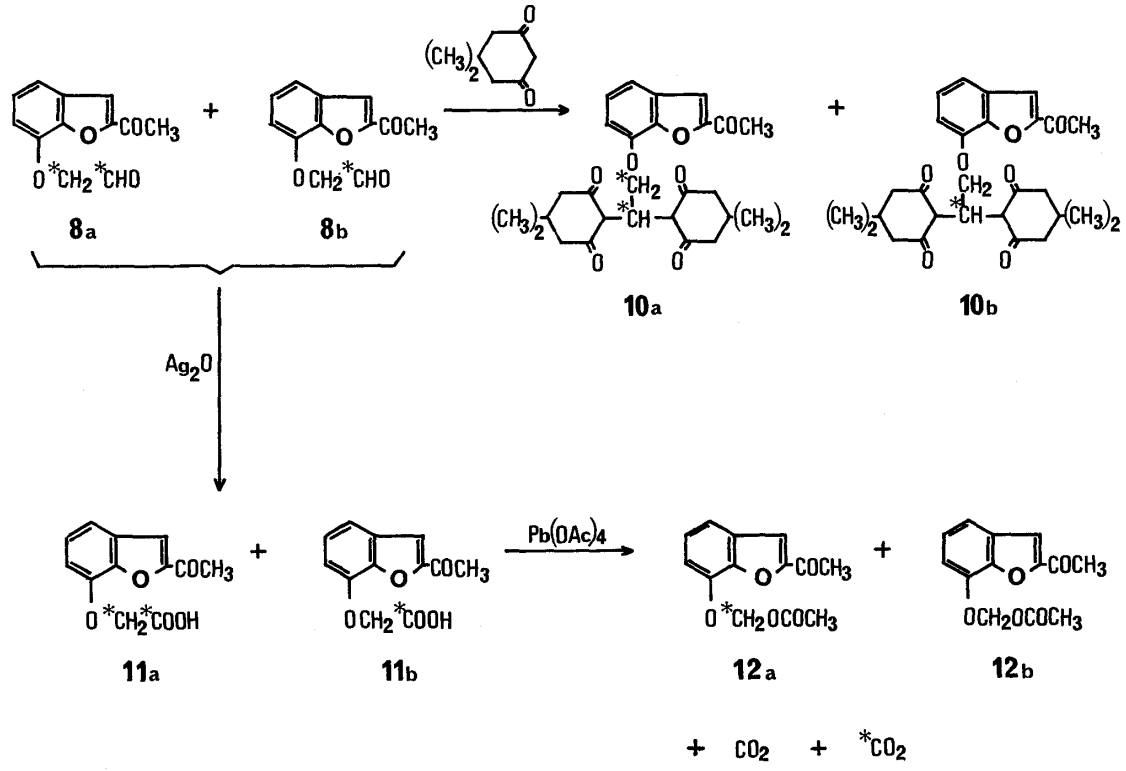

Chart 4

The radiochemical recoveries of methylenebisdimedone (**9a**+**9b**) and the carboxylic acid (**11a**+**11b**) were 27.8 and 68.1%, respectively, on the basis of the glycol (**7a**+**7b**).

These results showed that the radioactivity of the radioactive carbon of the carboxylic acid (**11b**) was 27.8% and the radioactivities in each radioactive carbon of the carboxylic acid (**11a**) were 20.2%[18] on the basis of the whole radioactivity of the glycol (**7a**+**7b**). Therefore, the radioactivity of the α-methylene carbon of the radioactive regio-isomeric carboxylic acid (**11a**) would be expected to comprise 29.7% of the whole radioactivity of **11a**+**11b**.[19]

The second oxidative cleavage was performed as follows: the carboxylic acid (**11a**+**11b**) with a specific radioactivity of 0.08185 μCi/mmol was decarboxylated by refluxing in benzene in the presence of lead tetraacetate to give 2-acetyl-7-acetoxymethoxybenzo[*b*]furan (**12a**+**12b**), which was purified by preparative TLC on silica gel and recrystallizations. Its specific radioactivity was 0.02377 μCi/mmol and the recovery was 29.0%, which is close to the

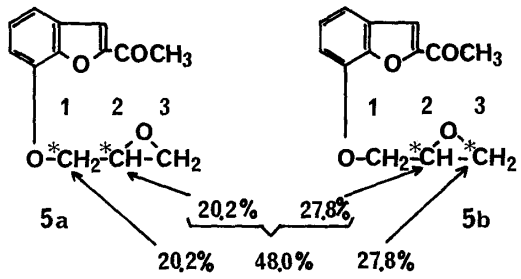

Fig. 1. Distribution of Radioactivity on the Propoxy Carbons of **5a**+**5b**

expected value, 29.7%, as mentioned above.

Therefore, the distribution of radioactivity on the three propoxy carbons of the oxirane (**5a**+**5b**) was confirmed rationally by means of stepwise cleavages of the three-carbon chains of **5a**+**5b**. The distribution of radioactivity at C-1, C-2 and C-3 of the oxirane (**5a**+**5b**) could be calculated as 20.2, 48.0 and 27.8% of the whole radioactivity of the oxirane (**5a**+**5b**), respectively (Fig. 1).

We could thus conclude that the oxirane (**5a**+**5b**) was a mixture of **5a** and **5b** in the ratio of 5/7 and therefore, it was clarified that the reaction of hydroxybenzo[*b*]furan potassium salt (**3**) with epichlorohydrin (**4**) proceeded competitively through path a (attack at C-1 of **4**) and path b (attack at C-3 of **4**) in the ratio of 5/7.

In earlier studies,[7-9] 3-bromo-1,2-epoxybutane and 1-bromo-2,3-epoxybutane, which are similar in structure to epichlorohydrin were used to investigate the reaction mechanism of epichlorohydrin with nucleophiles and it was concluded that one of the paths (path a or path b) or both were involved. Recently there was an interesting report that epibromohydrin [^{14}C-3] reacts with 1-naphthol to give 1,2-epoxy-3-(1-naphthyloxy)-propane [^{14}C-1] as a sole product, which suggested the attack of 1-naphthol exclusively at the bromine-bearing carbon of epibromohydrin (path a).[20] Further, McClure and his coworkers reported the reactions of chiral epichlorohydrin with phenolates.[10]

Because of these apparently conflicting reports, we tried to elucidate the reaction mechanism by means of direct methods. By using radiochemical tracer techniques, we demonstrated conclusively that epichlorohydrin reacts with hydroxybenzo[*b*]furan (**3**) to give phenyl glycidyl ether (**5a**+**5b**) through two different paths (path a and path b) competitively, not through a single path.

Experimental

Nonradioactive compounds (**5**, **7**, **8**, **9**, **10**, **11** and **12**) were synthesized in the same way as the corresponding radioactive compounds prior to the syntheses of the radioactive compounds, and the structures of all of them were confirmed by infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR) and elemental analysis. All radioactive compounds (**5a**+**5b**, **7a**+**7b**, **8a**+**8b**, **9a**+**9b**, **10a**+**10b**, **11a**+**11b** and **12a**+**12b**) were identified by comparing their melting points and TLC with those of the corresponding nonradioactive compounds. The cleavage reactions were carried out using radioactive compounds diluted with the corresponding nonradioactive compounds. Specific radioactivities were measured on a Packard Model 3000 series liquid scintillation spectrometer using toluene scintillator (toluene 1 l, 2,5-diphenyloxazole (PPO) 4 g, phenyloxazolylphenyloxazolylphenyl (POPOP) 0.1 g) and the measurements were repeated at least once. ^{1}H-NMR spectra were recorded with a Varian A-60 spectrometer (using tetramethylsilane (TMS) as an internal standard). The following abbreviations were used: s, singlet; br s, broad singlet; d, doublet; m, multiplet. IR spectra were recorded with a Shimadzu IR-27G spectrometer. All melting points were measured with a Thomas Hoover capillary melting point apparatus, and are uncorrected.

2-Acetyl-7-(2-hydroxy-3-isopropylaminopropoxy)benzo[*b*]furan[7-(1,2-^{14}C)] (6a),-[7-(2,3-^{14}C)] (6b)—Epichlorohydrin[1,2-^{14}C] (**4**) (56.9 mg, 0.618 mmol, specific radioactivity 11.41 mCi/mmol) was added to a solution of **3** (132 mg, 0.618 mmol) in dry dimethylformamide (3 ml) under a nitrogen atmosphere. This mixture was stirred at 70 °C for 1 h, then the solvent was evaporated off under reduced pressure, and the residue was treated with 30 ml of ethanol–ether solution. After removal of insoluble materials by filtration, the filtrate was concentrated to give crude crystalline oxirane (**5a**+**5b**). A small portion of the oxirane (**5a**+**5b**) was purified by preparative TLC (on silica gel,

5% ethanol in benzene) and recrystallization from ethanol. The radiochemical purity of the crystallized product was shown to be 97.5% by TLC and autoradiography. The specific radioactivity was 11.45 mCi/mmol. A mixture of the crude oxirane (**5a**+**5b**) and 0.14 ml of isopropylamine in ethanol (7 ml) was refluxed for 40 min. The solvent was evaporated off under reduced pressure, and the residue was purified by preparative TLC (on silica gel, aqueous ammonia : ethanol : benzene = 0.3 : 8 : 32) to yield 79.7 mg of **6a**+**6b**.

5a+**5b**: mp 81—83 °C, *Rf* value in TLC 0.56 (on silica gel, 2% ethanol in benzene). **6a**+**6b**: mp 113—115 °C, *Rf* value in TLC 0.65 (on silica gel, aqueous ammonia : ethanol : benzene = 0.3 : 8 : 32). These data were consistent with those of authentic samples.[13]

2-Acetyl-7-(2,3-dihydroxypropoxy)benzo[*b*]furan (7a+7b)——A solution of **5a**+**5b** (511.6 mg, specific radioactivity 2.545 μCi/mmol) in acetone (8.5 ml) was treated with 25% H_2SO_4 (4 ml) at 11 °C. The reaction mixture was stirred at 24 °C for 1 h. After addition of H_2O (20 ml), the whole was extracted with chloroform. The chloroform extract was washed with brine and dried over $MgSO_4$. The product (496 mg), obtained by removal of the solvent under reduced pressure, was purified by column chromatography (on silica gel, 10% ethanol in benzene) to furnish **7a**+**7b** (308 mg, 55.9%, specific radioactivity 2.427 μCi/mmol, recovery 95.4%). Colorless needles; mp 87—89 °C, *Rf* value in TLC 0.52 (on silica gel, 10% ethanol in benzene).

Nonradioactive Glycol (**7**): mp 87—89 °C, *Rf* value in TLC 0.52 (on silica gel, 10% ethanol in benzene). IR ν_{max}^{KBr} cm^{-1}: 3450, 1667, 1566, 1491, 1067. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s, $-COCH_3$), 3.50 (2H, br s, OH × 2), 3.78—3.94 (2H, m, $-CH_2OH$), 4.17—4.32 (3H, m, $-CH_2CH(OH)-$), 6.82—7.31 (3H, m, ring H), 7.40 (1H, s, ring C_3–H). *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.66; H, 5.53. Found: C, 62.39; H, 5.64.

Cleavage of the C_2–C_3 Bond of the Glycol (**7a**+**7b**): The glycol (**7a**+**7b**) (800 mg, 3.2 mmol, specific radioactivity 0.8472 μCi/mmol) was added to 12.5% $NaIO_4$ aqueous solution (28 ml) in portions at room temperature under stirring. The mixture was stirred for 0.5 h at room temperature, then cooled to −20 °C to afford a colorless solid (700 mg), 2-acetyl-7-formylmethoxybenzo[*b*]furan (**8a**+**8b**). Colorless powder; mp 122—125 °C, *Rf* value in TLC 0.72 (on silica gel, 10% ethanol in benzene).

Nonradioactive Aldehyde (**8**):[21] mp 122—125 °C, *Rf* value in TLC 0.72 (on silica gel, 10% ethanol in benzene). IR ν_{max}^{KBr} cm^{-1}: 3420, 1747, 1670. ^{1}H-NMR (acetone-d_6) δ: 2.56 (3H, s, $-COCH_3$), 5.05 (2H, br s, $-OCH_2-$), 6.95—7.46 (3H, m, ring H), 7.58 (1H, s, ring C_3–H), 9.56 (1H, br s, –CHO).

After filtration of the reaction mixture, the filtrate was washed with ether (20 ml). Dimedone (1 g) was added to the filtrate under stirring, then the mixture was allowed to stand overnight at room temperature to precipitate methylenebisdimedone (**11a**+**11b**) as a colorless solid. Recrystallization from methanol–benzene gave colorless prisms (405 mg, 43.8%, specific radioactivity 0.2351 μCi/mmol, recovery 27.8%); mp 190—191 °C (lit., 191.0—191.5 °C),[17] *Rf* value in TLC 0.91 (on silica gel, 10% ethanol in benzene).

Nonradioactive Methylenebisdimedone (**9**): mp 190—191 °C, *Rf* value in TLC 0.91 (on silica gel, 10% ethanol in benzene). IR ν_{max}^{KBr} cm^{-1}: 2965, 1610, 1581, 1254. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (12H, s, CH_3 × 4), 2.30 (8H, s, $-COCH_2-$ × 4), 3.16 (2H, br s, CH_2). *Anal.* Calcd for $C_{17}H_{24}O_4$: C, 69.79; H, 8.23. Found: C, 69.83; H, 8.27.

2-Acetyl-7-[{2,2-bis(5,5-dimethyl-1,3-dioxocyclohexan-2-yl)}ethoxy]benzo[*b*]furan (10a+10b)——A solution of **8a**+**8b** (250 mg) in acetone (45 ml) was treated with dimedone (371.5 mg) at 20 °C. The mixture was stirred at 25 °C for 1.5 h. Removal of acetone under reduced pressure gave a product (275 mg), which was recrystallized from ethanol to furnish **10a**+**10b** (255 mg), pale yellow prisms; mp 182—184 °C, *Rf* value in TLC 0.88 (on silica gel, 10% ethanol in benzene).

Nonradioactive **10**: mp 182—184 °C, *Rf* value in TLC 0.88 (on silica gel, 10% ethanol in benzene). IR ν_{max}^{KBr} cm^{-1}: 2940, 1678, 1596, 1080. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (12H, s, CH_3 × 4), 2.33 (8H, s, $-CH_2-$ × 4), 2.57 (3H, s, $-COCH_3$), 4.61—4.92 (3H, m, $-OCH_2CH<$), 6.83—7.30 (4H, m, ring H). *Anal.* Calcd for $C_{28}H_{32}O_7$: C, 69.95; H, 6.82. Found: C, 69.69; H, 7.10.

2-Acetyl-7-carboxymethoxybenzo[*b*]furan (11a+11b)——A mixture of **8a**+**8b** (300 mg), Ag_2O (318 mg) and 0.35 N NaOH aqueous solution (25 ml) was stirred at room temperature for 5.5 h. The resulting precipitate was removed by filtration, then the filtrate was acidified with 5% HCl and extracted with ether. The ethereal extract was washed with brine, dried (Na_2SO_4) and concentrated to yield pale yellow prisms, which were purified by preparative TLC (on silica gel, $CHCl_3$: MeOH : AcOH = 15 : 4 : 1) to give prisms. The prisms were recrystallized from ethanol. Colorless prisms (30 mg, specific radioactivity: 0.5773 μCi/mmol, recovery 68.1% based on **7a**+**7b**); mp 165—167 °C, *Rf* value in TLC 0.55 (on silica gel, $CHCl_3$: MeOH : AcOH = 15 : 4 : 1).

Nonradioactive Carboxylic Acid (**11**): mp 165—167 °C, *Rf* value in TLC 0.55 (on silica gel, $CHCl_3$: MeOH : AcOH = 15 : 4 : 1). IR ν_{max}^{KBr} cm^{-1}: 2970, 1740, 1662 , 1570. ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s, $-COCH_3$), 4.97 (2H, s, $-OCH_2-$), 5.88 (1H, br s, OH), 6.87—7.44 (4H, m, ring H). *Anal.* Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.50; H, 4.33.

2-Acetyl-7-acetoxymethoxybenzo[*b*]furan (12a+12b)——A mixture of **11a**+**11b** (200 mg, specific radioactivity: 0.08185 μCi/mmol), $Pb(OAc)_4$ (1.9 g) and dry benzene (35 ml) was refluxed for 1 h with stirring. Removal of the solvent by evaporation gave a residue, which was extracted with acetone (15 ml). The acetone solution was concentrated to give a yellow gum, which was purified by preparative TLC (on silica gel, 10% ethanol in benzene) and by recrystallization from ethanol. Pale yellow plates (50 mg, specific radioactivity: 0.02377 μCi/mmol, recovery 29.0%

based on **11a**+**11b**); mp 78—79 °C, *Rf* value in TLC 0.39 (on silica gel, 5% ethanol in benzene). IR ν_{max}^{KBr} cm^{-1}: 1764, 1682, 1563, 1019. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s, $-COCH_3$), 2.62 (3H, s, $-OCOCH_3$), 5.97 (2H, s, $-OCH_2-$), 7.17—7.52 (4H, m, ring H). *Anal.* Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 63.01; H, 4.90.

Acknowledgement The authors are grateful to Professor E. Fujita, Kyoto University, and Professor T. Fujita, Tokushima University, for valuable advice and discussions during this work. The authors also wish to thank Mr. Y. Fujiwara, Kyoto College of Pharmacy, for the measurement of NMR spectra.

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11) Epichlorohydrin [^{14}C-1,2] was purchased from The Radiochemical Centre Ltd., Amersham, England. Epichlorohydrin [^{14}C-1,2] was prepared in the following manner: acetylene-^{14}C[U] was treated with nickel carbonyl in the presence of methanol and hydrochloric acid to give methyl acrylate [^{14}C-2,3]. This was chlorinated to give methyl 2,3-dichloropropionate [^{14}C-2,3], which was purified by preparative gas-liquid chromatography (PGLC). Reduction of the dichloropropionate with lithium aluminium hydride gave 2,3-dichloropropanol [^{14}C-2,3] which was converted to epichlorohydrin [^{14}C-1,2] by reaction with aqueous sodium hydroxide according to the procedure of P. B. D. de la Mare and J. G. Pritchard, *J. Chem. Soc.*, **1954**, 1644. The product was finally purified by PGLC. Radiochemical purity (by gas-liquid radiochromatography on Carbowax 20 M column); >98%. Chemical purity (by gas-liquid chromatography on a Carbowax 20 M column); >98%.
12) These radiochemical regio-isomers were not separated. The symbol "**5a**+**5b**" represents the mixture of two radiochemical regio-isomers. ^{14}C-labelled positions are shown as *C in representations of the structures in Charts.
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21) The aldehyde (**8**) was also prepared by the following method: a solution of the unlabelled glycol (**7**) (250 mg) in dry benzene (40 ml) was added to a suspension of Pb $(OAc)_4$ (633 mg) in dry benzene (20 ml). The mixture was vigorously stirred for 0.5 h at room temperature, then H_2O (100 ml) was added. The benzene layer was washed and dried over Na_2SO_4. The benzene was evaporated off and the residue was recrystallized from ethanol to give 92 mg of the aldehyde (**8**).