A CONVENIENT SYNTHESIS OF 3-HYDROXY-4*H*-PYRAN-4-ONE DERIVATIVES HAVING A HALO OR HYDROXY GROUP AT THE 5-POSITION

Hisashi Takao,*[a] Yoshinori Endo,[a] and Tokunaru Horie[b]
Naruto Research Center, Otsuka Chemical Company, Satoura, Naruto, 772, Japan;[a] Department of Chemical Science and Technology, Faculty of Engineering, The University of Tokushima, Minamijosanjima, Tokushima 770, Japan[b]

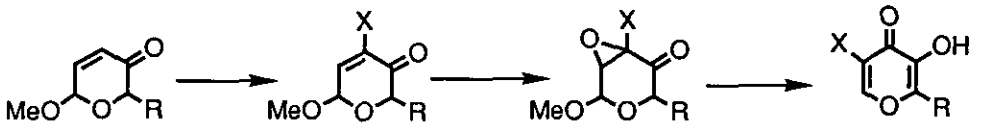
Abstract---The reaction of 4,5-epoxy-4-halo-6-methoxy-2-methyltetrahydropyran-3-ones (**4b** and **5b**) in acidic media was examined and the following results were found: The reaction of **4b** or **5b** with 1% sulfuric acid afforded a mixture of 3,5-dihydroxy-4*H*-pyran-4-one (**1b**) and 5-halo-3-hydroxy-4*H*-pyran-4-one (**2b** or **3b**), but the use of concentrated acid formed the corresponding 5-halo-4*H*-pyran-4-one (**2b** or **3b**) only. The reaction was applicable for a general method for synthesizing 3,5-disubstituted 4*H*-pyran-4-ones (**1**, **2**, and **3**).

Various studies of 4*H*-pyran-4-one derivatives have been reported in connection with natural products,[1,2] but those of 5-substituted 3-hydroxy-4*H*-pyran-4-ones are few and their properties have not been clearly elucidated. For example, 3,5-dihydroxy-4*H*-pyran-4-one (**1b**) was synthesized by the pyrolysis of D-threo-2,5-hexodiulose,[3] but this method was not suitable for the synthesis because of low yield. Therefore, the synthesis of 5-substituted 3-hydroxy-4*H*-pyran-4-ones was studied first in order to survey their biological activities. In this paper, we wish to describe a convenient method for synthesizing 3-hydroxy-4*H*-pyran-4-ones (**1-3**) with a halo or hydroxy group at the 5-position and their derivatives.

Generally, it has been known that esters of α-haloglycidic acids, obtained from dihaloacetates and ketones by the Darzens reaction, are converted into α-haloketo ester or α-hydroxyketo ester by the pyrolysis[4] or solvolysis with

aqueous sodium hydrogencarbonate.[5] The result suggests that 5-halo-3-hydroxy- (**2** and **3**) and 3,5-dihydroxy-4*H*-pyran-4-ones (**1**) are synthesized from the corresponding 4,5-epoxy-4-halo-6-methoxytetrahydropyran-3-ones (**4** and **5**) which were easily obtained from 6-methoxy-2*H*-pyran-3(6*H*)-ones (**6**) by the halogenation and the following epoxidation with hydrogen peroxide in

Scheme 1



6a-c
a: R=H
b: R=Me
c: R=Et

7a-c: X=Cl
8a-c: X=Br

4a-c: X=Cl
5a-c: X=Br

1a-c: X=OH
2a-c: X=Cl
3a-c: X=Br

mild basic conditions as shown in Scheme 1. Actually, the pyrolysis of bromo epoxide (**5b**) at 190-200°C under a nitrogen atmosphere gave only 5-bromo-3-hydroxy-4*H*-pyran-4-one (**3b**)[6] as expected. The chloro epoxide (**4b**) was also converted into 5-chloro-3-hydroxy-4*H*-pyran-4-one (**2b**) by the pyrolysis, although the reactivity was lower than that of the bromo epoxide (**5b**) and the starting material was partly recovered under the same conditions. Treatment of **4b** and **5b** with aqueous sodium hydrogencarbonate or pyridine afforded many byproducts and the yield of desired 3,5-dihydroxy-4*H*-pyran-4-one (**1b**) was below 10% because of low stability of the starting materials in the basic media. Therefore, the reaction of the halo epoxides (**4b** and **5b**) in acidic media was examined in detail.

The reaction of **4b** with 1% sulfuric acid at 60-65°C afforded a mixture of 5-chloro-3-hydroxy- (**2b**) and 3,5-dihydroxy-4*H*-pyran-4-ones (**1b**), and the ratio of the two products was constant in the reaction period (*ca.* 1:2) as shown in Figure 1. The ratio was not changed by the variation of reaction temperature and the rising of the temperature accelerated the rate without the formation of byproducts. The similar phenomena were observed in the reaction of the 4-bromo epoxide (**5b**), but the ratio of **3b** to **1b** was higher than that in the reaction of **4b** (*ca.* 1.3:1). These results suggest that the

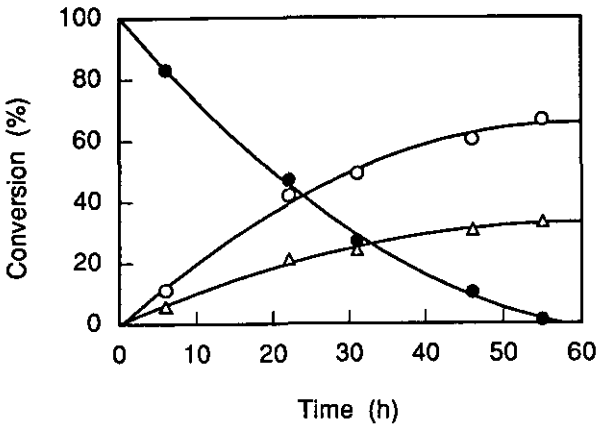


Figure 1 Time course of the reaction of **4b** with 1% sulfuric acid at 60-65°C; **4b**: ●, **1b**: ○, **2b**: △.

Table 1 Reaction Conditions of 4,5-Epoxy-4-halo-6-methoxytetrahydropyran-3-ones (**4b** and **5b**) and Product Ratios

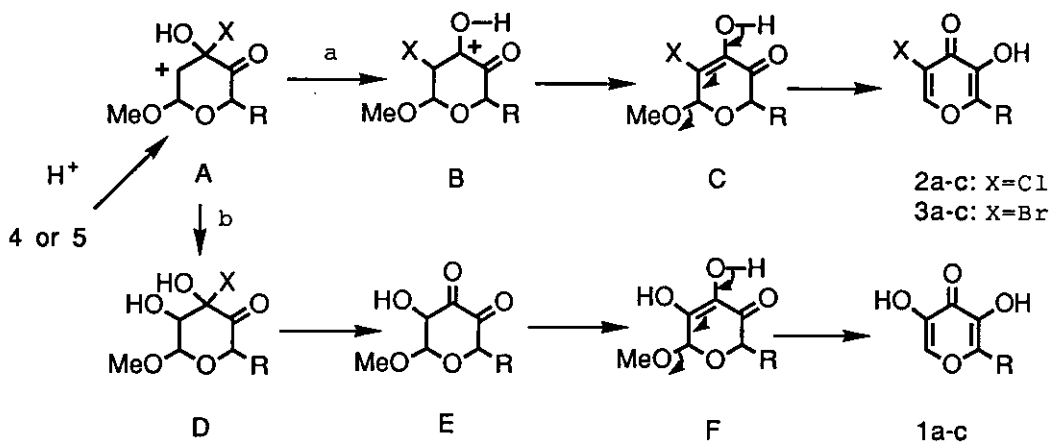
Starting material	Conditions				Products			
	Acid		Additive (5 equiv.)	Time (h)	Yield (%)	Relative ratio (%) 1b	2b	3b
4b	1%	H_2SO_4	-	6	61	67	33	-
5b	1%	H_2SO_4	-	6	61	57	-	43
4b	10%	H_2SO_4	-	3	66	66	34	-
5b	10%	H_2SO_4	-	3	68	37	-	63
4b	50%	H_2SO_4	-	3	67	54	46	-
5b	50%	H_2SO_4	-	3	65	-	-	100
4b	35%	HCl	-	3	82	-	100	-
4b	47%	HBr	-	3	65	-	-	100
4b	10%	H_2SO_4	NaCl	3	83	-	100	-
4b	10%	H_2SO_4	NaBr	3	82	-	-	100

rearrangement and solvolysis with acid catalyst proceed simultaneously in the reaction and the rates of the two reactions are dependent on the migratory aptitude of a halogen atom and on pH of the reaction media. Therefore, the effects of the acid strength of the reaction medium and the halide ion were additionally examined as shown in Table 1.

The ratio of **1b** increased with decreasing the acid concentration and that of

2b or **3b** decreased. The results show that the two reactions proceed simultaneously as shown in Scheme 2. That is, acid-catalyzed ring opening of the halo epoxide (**4** or **5**) brings about the formation of cation (**A**), which is transformed to the intermediates (**B** and **D**) by a halogen migration (path a) and an attack of a hydroxide ion (path b). The two intermediates (**B** and **D**) lead to the halogeno (**2** or **3**) and hydroxy compounds (**1**) *via* the enol forms (**C** and **F**) of the corresponding diketone derivatives, respectively. The rates of the two reactions (paths a and b) are dependent on the acid strength and migratory aptitude of the halogen atom. When the reaction is carried out in the low concentration of sulfuric acid, the path a is retarded because the path b is accelerated by the increasing concentration

Scheme 2

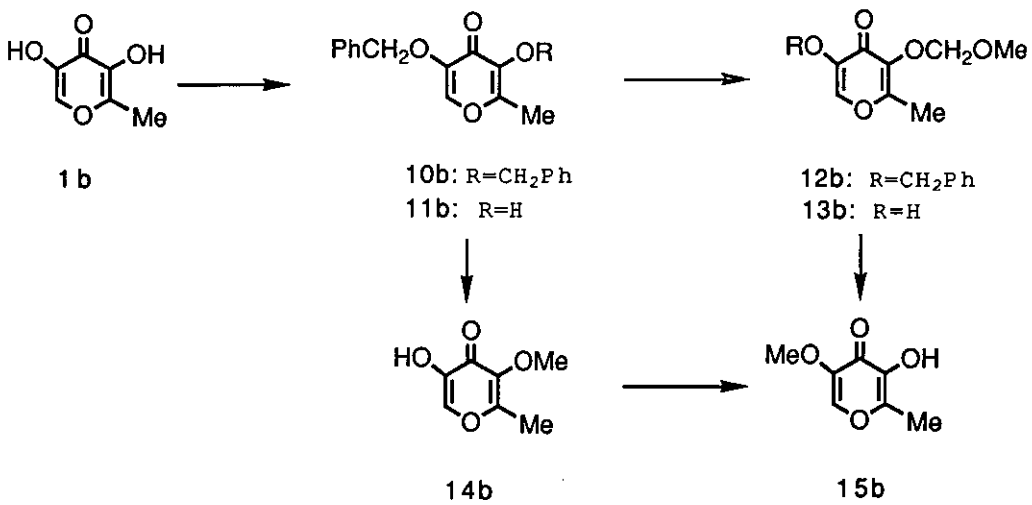


of hydroxide ion and the ratio of **1b** by the solvolysis increases in result. The reason why the ratio of **1b** in the product from **4b** is higher than that from **5b** seems to be that the migratory aptitude of the chloride ion is lower than that of the bromide. When the reaction was conducted under high concentration of a halide ion, the anion attacks predominantly on the cation (**A**). Actually, the reaction in the concentrated mineral acid or in the presence of sodium bromide or chloride suppressed completely the formation of **1b** as shown in Table 1, although the reaction upon the addition of potassium iodide afforded many intractable byproducts.

These results show that the reaction of halo epoxides (**4b** and **5b**) is applicable for a general method for synthesizing 3-hydroxy-4*H*-pyran-4-ones (**1-3**) with a halo or hydroxy group at the 5-position. Actually, the similar phenomena were observed in the reaction of the other halo epoxides, and the 3,5-dihydroxy-4*H*-pyran-4-ones (**1a** and **1c**) which led to diacetates (**9a** and **9c**) and 5-halo-3-hydroxy-4*H*-pyran-4-ones (**2a**, **3a**, **2c**, and **3c**) were easily obtained by the application of the reactions as shown in Table 2 (see EXPERIMENTAL).

Additionally, partial alkylation of **1b** was examined in order to eatablish a method for the chemical modification of the 3- and/or 5-hydroxy groups in **1**. Since the selectivity of the partial dealkylation is generally higher than that of the partial alkylation in the studies of polyhydroxyflavone derivatives,[9] the partial alkylation route as shown in Scheme 3 was examined.

Scheme 3



The 3-benzyloxy group in dibenzyl ether (**10b**) of **1b** was selectively cleaved with hydrochloric acid in acetic acid to give 5-benzyloxy-3-hydroxy-2-methyl-4*H*-pyran-4-one (**11b**). The ^{1}H nmr spectra of **11b** exhibited the existence of a benzyloxy group and the NOE was observed in the C_6-proton by irradiation of the benzylmethylene group. The methoxymethylation of **11b** formed the 3-methoxymethyl ether (**12b**) which was hydrogenolyzed with

palladium on charcoal to give 5-hydroxy-3-methoxymethoxy-2-methyl-4*H*-pyran-4-one (**13b**). The ethers (**11b** and **13b**) were useful for the selective alkylation of the 3- or 5-hydroxy group in **1b**, and the 3- and 5-methyl ethers (**14b** and **15b**) were synthesized by the methylation followed by removal of the protecting group. The method may be widely applicable to the chemical modification of the hydroxy groups in 3,5-dihydroxy-4*H*-pyran-4-ones (**1**).

EXPERIMENTAL

All melting points were uncorrected. ^{1}H Nmr spectra were recorded on a Hitachi R-24B spectrometer (60 MHz) using tetramethylsilane as an internal standard and chemical shifts were given in δ values. Gas chromatographic analyses were conducted at 120-160°C with a Shimadzu GC-7A chromatograph equipped with a column (100 x 0.635 cm) of thermon 3000 (Shimalite TPA, 60-80 mesh). Elemental analyses were performed with a Yanaco CHN corder Model MT-2. 4-Halo-6-methoxy-2*H*-pyran-3(6*H*)-ones (**7** and **8**) were easily synthesized from furfuryl alcohols *via* 6-methoxy-2*H*-pyran-3(6*H*)-ones (**6**) by the method of Brenman *et al.*[10]

4,5-Epoxy-4-halo-6-methoxytetrahydropyran-3-ones (4 and 5): To a mixture of **7** or **8** (0.1 mol) and 30% hydrogen peroxide (15 ml, 0.13 mol) in MeOH (100 ml) was added slowly 5% sodium carbonate (5 ml, 0.002 mol) at 5-10°C for 30 min, and then the mixture was stirred at 10-15°C for 2 h and neutralized with 1% HCl to pH 7. After removal of most of the MeOH, the residue was extracted with dichloromethane to give **4** or **5** in 83-90% yields. Compounds (**4b**, **4c**, **5b**, and **5c**) were a mixture of two stereoisomers (*ca.* 3:1) and were used in the next reaction without separation. **4a**: 84%, colorless needles, mp 65-66°C (from n-hexane) (lit.,[11] 67-68°C); ^{1}H nmr ($CDCl_3$) δ: 3.49 (3H, s, OCH_3), 3.80 (1H, d, *J*=1.6 Hz, C_5-H), 4.21 (2H, s, C_2-H), 5.08 (1H, d, *J*=1.6 Hz, C_6-H). **4b**: 90%, pale yellow oil, major isomer; ^{1}H nmr ($CDCl_3$) δ: 1.42 (3H, d, *J*=7.0 Hz, CH_3), 3.51 (3H, s, OCH_3), 3.80 (1H, d, *J*=1.2 Hz, C_5-H), 4.30 (1H, q, *J*=7.0 Hz, C_2-H), 5.02 (1H, d, *J*=1.2 Hz, C_6-H). Anal. calcd for $C_7H_9O_4Cl$: C, 43.65; H, 4.71. Found: C, 43.72; H, 4.62. **4c**: 83%, pale yellow oil, major isomer; ^{1}H nmr ($CDCl_3$) δ: 0.97 (3H, t, *J*=7.5 Hz, CH_3), 1.86 (2H, q, *J*=7.5 Hz, CH_2-), 3.48 (3H, s, OCH_3), 3.76 (1H, d, *J*=1.2 Hz, C_5-H), 3.88-4.20 (1H, m, C_2-H), 5.06 (1H, d, *J*=1.2 Hz, C_6-H). Anal. Calcd for $C_8H_{11}O_4Cl$: C, 46.96; H, 5.43. Found: C, 46.66; H, 5.26. **5a**: 88%, colorless needles, mp 125-126°C

(from n-hexane) (lit.,[11] 127-128°C); ^{1}H nmr ($CDCl_3$) δ: 3.50 (3H, s, OCH_3), 3.75 (1H, d, *J*=1.6 Hz, C_5-H), 4.18 (2H, s, C_2-H), 5.04 (1H, d, *J*=1.0 Hz, C_6-H). **5b**: 83%, pale yellow oil, major isomer; ^{1}H nmr ($CDCl_3$) δ: 1.40 (3H, d, *J*=7.0 Hz, CH_3), 3.50 (3H, s, OCH_3), 3.78 (1H, d, *J*=1.0 Hz, C_5-H), 4.30 (1H, q, *J*=7.0 Hz, C_2-H), 5.04 (1H, d, *J*=1.0 Hz, C_6-H). Anal. Calcd for $C_7H_9O_4Br$: C, 35.47; H, 3.83. Found. C, 35.46; H, 3.72. **5c**: 80%, pale yellow oil, major isomer; ^{1}H nmr ($CDCl_3$) δ: 1.02 (3H, t, *J*=7.5 Hz, CH_3), 1.80 (2H, q, *J*=7.5 Hz, CH_2-), 3.48 (3H, s, OCH_3), 3.78 (1H, d, *J*=1.2 Hz, C_5-H), 3.90-4.28 (1H, m, C_2-H), 5.10 (1H, d, *J*=1.2 Hz, C_6-H). Anal. calcd for $C_8H_{11}O_4Br$: C, 38.27; H,4.42. Found: C, 38.48; H, 4.35.

Hydrolysis of 4,5-epoxy-4-halo-6-methoxytetrahydropyran-3-ones (4 and 5): A mixture of **4** or **5** (0.01 mol) and 1-50% mineral acid (20 ml) was heated at 90-95°C for 3-6 h with stirring, and then treated with active carbon (1.0 g). The mixture was concentrated, and extracted with ethyl methyl ketone. The extract was dried over $MgSO_4$, concentrated, and diluted with dichloromethane. The insoluble materials were collected by filtration and recystallized from MeOH to give 3,5-dihydroxy-4*H*-pyran-4-ones (**1**) as colorless needles. The soluble materials were recrystallized from benzene to give 5-chloro-3-hydroxy-4*H*-pyran-4-ones (**2**) or 5-bromo-3-hydroxy-4*H*-pyran-4-ones (**3**) as colorless needles (Table 2).

Diacetates (9) of 1: Compounds (**1a-c**) were converted into the diacetates (**9**) by treating with acetic anhydride-pyridine at 90°C. **9a**: 81%, colorless needles, mp 113-114°C (from benzene-n-hexane) (lit.,[7] 113-114°C). Anal. Calcd for $C_9H_8O_6$: C,50.95; H,3.80. Found: C, 50.88; H, 3.62. **9b**: 89%, colorless needles, mp 97-99°C (from benzene-n-hexane) (lit.,[12] 102-102.5°C). Anal. Calcd for $C_{10}H_{10}O_6$: C, 52.91; H, 4.44. Found: C, 53.12; H, 4.42. **9c**: 88%, pale yellow oil. Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.72; H, 5.04.

Pyrolysis of 4-bromo-4,5-epoxy-6-methoxytetrahydropyran-3-one (5b): Compound (**5b**) (1.2 g, 0.005 mol) was pyrolyzed at 190-200°C under a nitrogen atmosphere for 30 min. The resulting red brown oil was extracted with chloroform, washed with brine, and dried over $MgSO_4$. The extract was evaporated, and the residue was recrystallized from benzene to give **3b** (640 mg, 62%) as pale yellow needles.

Table 2 Solvolysis of 4-Halo-6-methoxy-4,5-epoxytetrahydropyran-3-ones (4 and 5) and Analytical Data for the Products

Starting material	Acid	Compd	Yield (%)	mp (°C)	^{1}H Nmr (DMSO-d_6) C_2-H	C_6-H	Formula	Found (Calcd) C	H
4a	1% H_2SO_4	1a	20	201-202 (203.5)[7]	7.90	7.90	$C_5H_4O_4$	46.88 (46.76	3.15 3.13)
		2a	25	124-125	8.16	8.59			
4b	1% H_2SO_4	1b	41	181-183 (184-184.5)[8]	-	7.90	$C_6H_6O_4$	50.51 (50.71	4.12 4.26)
		2b	20	112-113	-	8.44			
4c	1% H_2SO_4	1c	36	127-128	-	7.90	$C_7H_8O_4$	54.12 (53.85	5.05 5.16)
		2c	22	104-105	-	8.44			
4a	35% HCl	2a	65	124-125	8.16	8.59	$C_5H_3O_3Cl$	41.01 (40.98	1.94 2.06)
4b	35% HCl	2b	82	112-113	-	8.44	$C_6H_5O_3Cl$	44.78 (44.89	2.87 3.14)
4c	35% HCl	2c	72	104-105	-	8.44	$C_7H_7O_3Cl$	48.21 (48.16	3.95 4.04)
5a	50% H_2SO_4	3a	63	148-150	8.11	8.57	$C_5H_3O_3Br$	31.44 (31.67	1.58 1.62)
5b	50% H_2SO_4	3b	65	145-147 (148-151)[6]	-	8.50	$C_6H_5O_3Br$	35.18 (35.15	2.30 2.46)
5c	50% H_2SO_4	3c	70	128-129	-	8.50	$C_7H_7O_3Br$	38.46 (38.38	3.12 3.22)

3,5-Dibenzyloxy-2-methyl-4*H*-pyran-4-one (10b): A mixture of **1b** (2.84 g, 0.02 mol), benzyl chloride (6.3 g, 0.05 mol) and anhydrous potassium carbonate (6.5 g, 0.05 mol) in dry DMF (30 ml) was heated at 95-100°C for 8 h with vigorous stirring. The cooled reaction mixture was diluted with water, and extracted with benzene. The extract was washed with brine, dried over $MgSO_4$, and then evaporated. The residue was recrystallized from MeOH to give dibenzyl ether (**10b**) (4.5 g, 70%) as colorless needles, mp 99-101°C; ^{1}H nmr ($CDCl_3$) δ: 2.04 (3H, s, CH_3), 5.07, 5.15 (each 2H, s, OCH_2-), 7.30 (10H, s, Ar-H), 7.43 (1H, s, C_6-H). Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.79; H, 5.76.

5-Benzyloxy-3-hydroxy-2-methyl-4*H*-pyran-4-one (11b): Compound (**10b**) (9.7 g, 0.03 mol) was dissolved in acetic acid (100 ml) containing conc. HCl (30 ml) and then stirred at 60°C for 10 h. The mixture was diluted with water and

then extracted with chloroform. The extract was evaporated and the residue was recrystallized from benzene-n-hexane to give **11b** (4.18 g, 60%) as colorless needles, mp 133-134°C; ^{1}H nmr ($CDCl_3$) δ: 2.14 (3H, s, CH_3), 5.12 (2H, s, OCH_2-), 7.30 (5H, s, Ar-H), 7.48 (1H, s, C_6-H). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.36; H, 5.02.

5-Hydroxy-3-methoxymethoxy-2-methyl-4*H*-pyran-4-one (13b): To a mixture of 60% NaH (0.45 g, 0.01 mol) and **11b** (2.23 g, 0.01 mol) in dry DMF (10 ml) was added methoxymethyl chloride (0.88 g, 0.011 mol) below 10°C. The mixture was stirred at room temperature for 3 h, then diluted with water, and extracted with ether. The extract was washed with 1% HCl, and brine, dried over $MgSO_4$, and evaporated to give the crude methoxymethyl ether (**12b**) (2.48 g) as oil. The crude product was hydrogenolyzed with 10% Pd-C (100 mg) in MeOH (20 ml) until the uptake of hydrogen ceased. After the catalyst was filtered off, the filtrate was evaporated. The residue was recrystallized from MeOH to give **13b** (1.49 g, 80%) as colorless needles, mp 91-92°C; ^{1}H nmr ($CDCl_3$) δ: 2.38 (3H, s, CH_3), 3.52 (3H, s, OCH_3), 5.22 (2H, s, OCH_2-), 6.96 (1H, br s, OH), 7.78 (1H, s, C_6-H). Anal. Calcd for $C_8H_{10}O_5$: C, 51.61; H, 5.41. Found: C, 51.69; H, 5.29.

5-Hydroxy-3-methoxy-2-methyl-4*H*-pyran-4-one (14b): A mixture of **11b** (552 mg, 23 mmol), methyl iodide (400 mg, 30 mmol) and anhydrous potassium carbonate (320 mg, 23 mmol) in acetone (10 ml) was refluxed for 5 h with vigorous stirring, and then water was added. The oily products were extracted with ethyl acetate. The extract was washed with 5% $NaHCO_3$, then brine, and dried over $MgSO_4$. The evaporation of the solvent afforded the crude methyl ether (490 mg) as oil. The crude product was hydrogenolyzed with 10% Pd-C (100 mg) and then recrystallized from benzene to give **14b** (280 mg, 90%) as colorless needles, mp 127-128°C; ^{1}H nmr ($CDCl_3$) δ: 2.32 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 7.18 (1H, br s, OH), 7.76 (1H, s, C_6-H). Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 54.05; H, 5.09.

3-Hydroxy-5-methoxy-2-methyl-4*H*-pyran-4-one (15b): A mixture of **13b** (930 mg, 50 mmol), methyl iodide (800 mg, 56 mmol) and anhydrous potassium carbonate (900 mg, 65 mmol) in acetone (20 ml) was refluxed for 6 h with vigorous stirring and treated in usual manner to give the crude methyl ether (920 mg) as oil. The crude product was refluxed with 20% HCl (5 ml) in MeOH (30 ml) for 2 h, and the mixture was diluted with water. The mixture was concen-

trated and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and then evaporated. The residue was recrystallized from MeOH to give **15b** (663 mg, 85%) as colorless needles, mp 169-171°C; ^1H nmr (DMSO-d_6) δ: 2.32 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 7.68 (1H, s, C_6-H), 7.98 (1H, br s, OH). Anal. Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 53.72; H, 4.93.

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