A Convenient Preparation of Salicylaldehydes from 2-Methylbenzofurans by Ozonolysis

Hisashi ISHII,*,[a] Shuji OHTA,[a] Hiromi NISHIOKA,[b] Naomi HAYASHIDA,[b] and Takashi HARAYAMA*,[b]

Faculty of Pharmaceutical Sciences, Chiba University,[a] 1–33 Yayoi-cho, Inage-ku, Chiba 263, Japan and Faculty of Pharmaceutical Sciences, Okayama University,[b] Tsushimanaka 1–1–1, Okayama 700, Japan.
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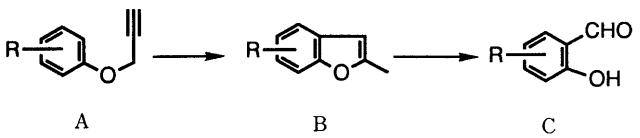
A convenient and effective transformation of 2-methylbenzofuran (B) to salicylaldehyde (C) was achieved by ozonolysis of B in CH_2Cl_2 at −78 °C followed by alkaline hydrolysis.

Keywords salicylaldehyde; 2-methylbenzofuran; ozonolysis; benzofuran ring cleavage; ruthenium tetroxide; osmium tetroxide

In the course of synthetic studies on chelerythrine (**1**), we succeeded in developing two new synthetic methods, *i.e.*, preparation of 2-methylbenzofuran (B) by the cesium fluoride (CsF)-mediated Claisen rearrangement of an aryl propargyl ether (A) and transformation of the 2-methylbenzofuran (B) to a salicylaldehyde (C) *via* oxidative cleavage of the fused furan ring with osmium tetroxide (OsO_4) and periodate, followed by alkaline hydrolysis.[1] These methods are suitable for preparing aromatic compounds with four successive substituents involving alkoxy group(s). By taking advantage of these methods, we achieved syntheses of chelerythrine (**1**),[2] lemaireocereine (**2**),[3] and coumarins (**3**[4] and **4**[5]). As reported in the previous paper,[1] a stoichiometric amount of OsO_4 was necessary for preparing C from B, since oxidation by the Lemiux–Johnson or Van Rheenen method using a catalytic amount of OsO_4 gave the desired dihydroxylation product only in a very poor yield. Therefore, we planned to investigate more effective and convenient methods for preparing C from B.

First, oxidation of a benzo[*b*]furan (cumaron) (**5**) with ruthenium tetroxide (RuO_4) prepared by the Sharpless method,[6] was investigated. Thus, oxidation of **5** with RuO_4 in aqueous acetonitrile at room temperature, without hydrolysis, gave salicylaldehyde (**6**) and salicylic acid (**7**) in 58% and 16% yields, respectively. Moreover, oxidation of 2-methylnaphthofuran (**8**)[1] with RuO_4 under the same conditions afforded 2-acetoxy-1-naphthaldehyde (**9**) and 1,2-naphthoquinone (**10**) in 23% and 26% yields, respectively. In order to examine the mechanism of formation of **10**, oxidation of 2-hydroxy-1-naphthaldehyde (**11**), which is the hydrolysis product of **9**, with RuO_4 was carried out, resulting in 21% recovery of **11** and no formation of **10**. This indicates at least that **10** is not an oxidation product derived from **11**, although the formation mechanism of **10** still remains to be clarified. Successive treatment of the benzofuran (**12**), which was prepared from the propargyl ether (**13**) by the CsF-mediated Claisen rearrangement, with RuO_4 and sodium hydrogen carbonate ($NaHCO_3$) solution gave 3-bromo-2-hydroxybenzaldehyde (**14**) and the ketone (**15**)[7] in 42% and 14% yields, respectively. Then, oxidation of the 2-methylbenzofuran derivatives (**16**,[1] **17**,[5] and **18**[3]) containing a methoxy group with RuO_4 was studied. However, oxidation was unfruitful, with the reaction mixture showing many spots on thin layer chromatography (TLC), and the starting material was recovered in 20—45% yield.



A B C

Chart 1

Next, another method was investigated for preparing the salicylaldehyde (C) by the oxidative cleavage of the furan ring in the benzofuran (B). Thus, since furan rings undergo oxidation with ozone,[8] ozonolysis was examined. Oxidation of **5** with ozone in CH_2Cl_2 at −78 °C followed by reduction of the ozonide with dimethyl sulfide afforded the expected salicylaldehyde (**6**)[9] in 67% yield. Oxidation of **8** gave **9** and **11** in 44% and 5% yields, respectively. Then, this convenient method was applied to several 2-methylbenzofurans (B) containing a methoxy group, which would be susceptible to oxidants such as RuO_4. The results of ozonolysis followed by hydrolysis are summarized in Table I in comparison with the old OsO_4 method.[1] In this connection, treatment of **12** with OsO_4 produced an unexpected product (**15**) in 70% yield, in spite of reduction of the osmate with sodium hydrogen sulfite.[1]

In conclusion, the present method using ozone would be very convenient and effective for preparing salicylaldehydes (C) from 2-methylbenzofurans (B).

TABLE I. Results of the Preparation of Salicylaldehyde (C) from 2-Methylbenzofuran (B) *via* Ozonolysis followed by Hydrolysis[a]

2-Methylbenzofuran (B)	Salicylaldehyde (C)	Yield (%)
12	**14**	79 (50)[b]
16	**21**	86[c] (74)[1]
17	**22**	74 (44)[5]
18	**23**	71 (71)[3]
19	**24**	43 (54)[2]
20	**25**	61 (43)[4]

a) Values in parentheses indicate the yields of C from B *via* dihydroxylation with OsO_4, periodate oxidation and hydrolysis. *b*) The value represents the yield of **14** *via* reduction of **15** with sodium borohydride and oxidation with $NaIO_4$, because oxidation of **12** with OsO_4 afforded the ketone (**15**). *c*) In this connection, ozonolysis of **16** without hydrolysis afforded the expected acetate of **21** in 89% yield.

Experimental

Melting points were measured on a micro melting point hot-stage

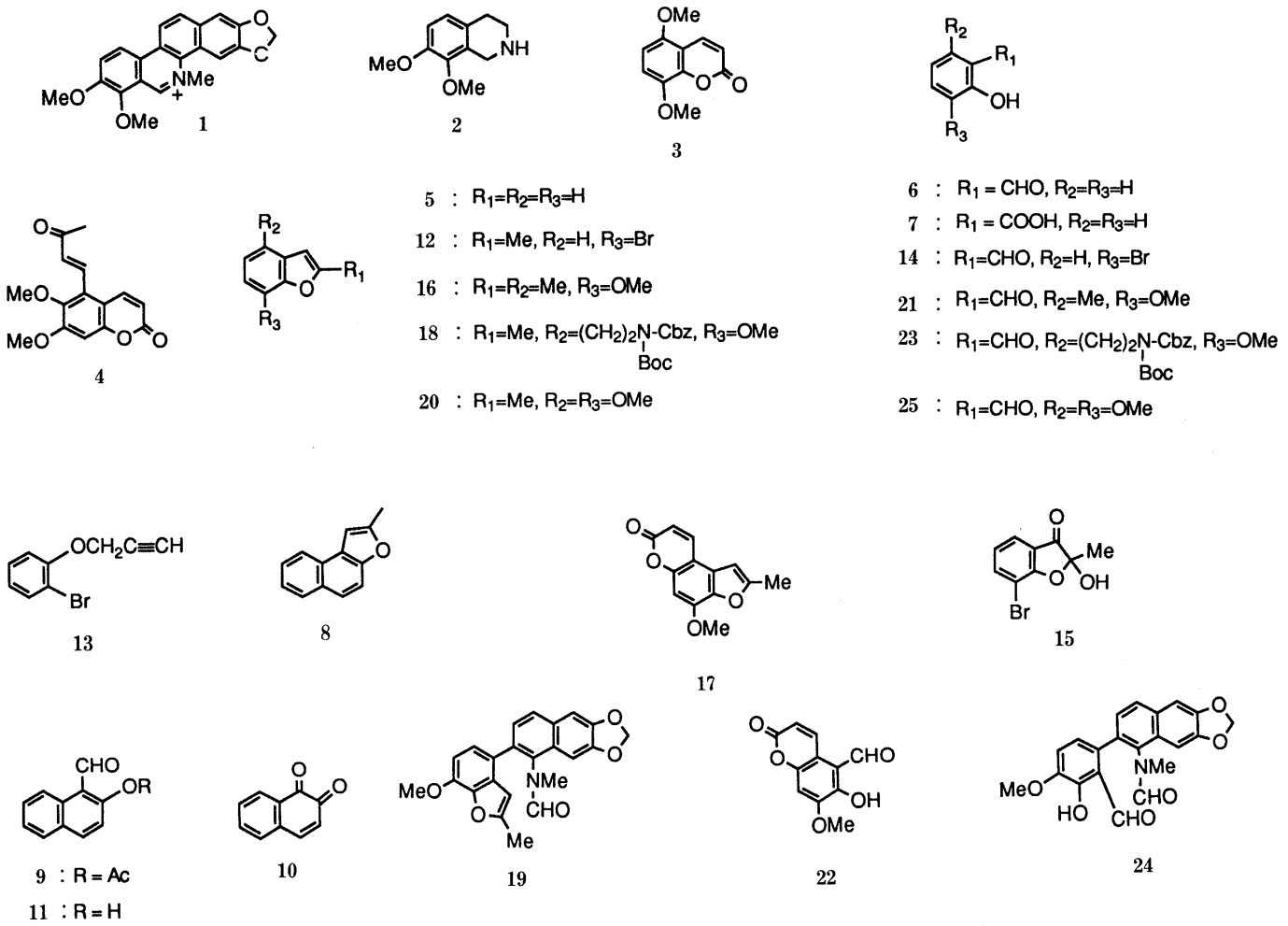


Chart 2

apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a Hitachi 215 spectrometer or JASCO A-102 and ^{1}H-NMR spectra in deuteriochloroform on Hitachi R-24B (60 MHz), Hitachi R-1500 (60 MHz), JEOL FX-270 (270 MHz), JEOL GSX-400 (400 MHz) and/or -500 (500 MHz) spectrometers, unless otherwise noted. The ^{1}H-NMR data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in hertz. Electron impact mass spectra (EIMS) were taken on a Hitachi M-60 or VG-70G spectrometer (direct inlet) at 70 eV. Column chromatography was carried out on silica gel (Merck, Silica gel 60, No. 7734 or No. 9385). In general, the extract was washed with brine, dried over anhydrous $MgSO_4$, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. CsF was heated and powdered under argon before use. Compounds for which no melting point is given are oily. The synthetic samples were identified by comparison of spectral (^{1}H-NMR and IR) data with those of commercial or synthetic authentic samples or by comparison with physical data in the cited references.

Oxidation of Benzofuran (5) with RuO_4 To a solution of **5** (0.500 g, 4.23 mmol) in CH_3CN (17 ml) was added a solution of $NaIO_4$ (3.712 g, 17.35 mmol) and ruthenium trichloride ($RuCl_3$) hydrate (0.021 g) in H_2O (12.7 ml). The mixture was stirred at room temperature for 1 h, poured into H_2O and then extracted with ether. The residue in $CHCl_3$ was chromatographed on silica gel (No. 7734). Elution with $CHCl_3$–AcOEt (10 : 1) gave the salicylaldehyde (**6**) (0.299 g, 58%). Fractions eluted with AcOEt and acetone were dissolved in AcOEt and extracted with 5% aqueous $NaHCO_3$ solution. The alkaline layer was acidified with 10% hydrochloric acid and extracted with AcOEt. The residue was recrystallized from $CHCl_3$–hexane to afford salicylic acid (**7**) (0.093 g, 16%), mp 160—162 °C (colorless needles).

Oxidation of 2-Methylnaphtho[2,1-*b*]furan (8) with RuO_4 A solution of $NaIO_4$ (0.963 g, 4.50 mmol) and $RuCl_3$ hydrate (0.006 g) in H_2O (3 ml) was added to a solution of **8** (0.200 g, 1.1 mmol) in CH_3CN (4.4 ml). The mixture was stirred at room temperature for 1 h, then diluted with H_2O, and extracted with CH_2Cl_2. The residue in $CHCl_3$ was chromatographed on silica gel (No. 7734) in the dark. Elution with $CHCl_3$ gave 2-acetoxy-1-naphthaldehyde (**9**) (0.054 g, 23%), mp 94—96 °C (lit.[10] mp 96—97 °C) (colorless plates from hexane). IR cm^{-1}: 1765 (C=O), 1685 (C=O). ^{1}H-NMR (60 MHz): 2.44 (3H, s, $OCOCH_3$), 7.27 (1H, d, J=8.9 Hz, C_3-H), 7.56 (1H, br t, J=7.1 Hz, C_6-H or C_7-H), 7.68 (1H, br t, J=7.1 Hz, C_6-H or C_7-H), 7.87 (1H, d, J=7.1 Hz, C_5-H), 8.10 (1H, d, J=8.9 Hz, C_4-H), 9.13 (1H, d, J=8.9 Hz, C_8-H), 10.71 (1H, s, CHO). MS m/z: 214 (M^+). Successive elution with $CHCl_3$ gave 1,2-naphthoquinone (**10**)[11] (0.045 g, 26%), mp 146—150 °C (lit.[12] mp 145—147 °C) (yellow prisms from benzene). IR cm^{-1}: 1660 (C=O). ^{1}H-NMR (500 MHz): 6.44 (1H, d, J=10.1 Hz, C_3-H), 7.38 (1H, d, J=7.3 Hz, C_5-H), 7.45 (1H, d, J=10.1 Hz, C_4-H), 7.52 (1H, t, J=7.3 Hz, C_6-H or C_7-H), 7.66 (1H, t, J=7.3 Hz, C_6-H or C_7-H), 8.11 (1H, d, J=7.3 Hz, C_8-H). MS m/z: 158 (M^+).

2-(2-Propynyloxy)bromobenzene (13) A mixture of *o*-bromophenol (35 g, 0.202 mol), propargyl bromide (33.7 g, 0.283 mol), and K_2CO_3 (39.1 g, 0.283 mol) in dimethylformamide (77 ml) was stirred at room temperature for 50 min. The reaction mixture was diluted with water and extracted with ether. The extract was washed with 5% aqueous NaOH solution and brine, and dried over K_2CO_3. The residue was distilled under reduced pressure to give **13** (37.2 g, 87%), bp 107—109 °C (6 mmHg). IR (neat) cm^{-1}: 3300 (≡CH), 2130 (C≡C). ^{1}H-NMR (60 MHz): 2.50 (1H, t, J=2.8 Hz, ≡CH), 4.70 (2H, d, J=2.8 Hz, $-OCH_2C$), 6.70—7.60 (4H, m, aromatic protons). MS m/z: 212 (M^++2), 210 (M^+).

7-Bromo-2-methylbenzo[*b*]furan (12) A suspension of **13** (3.0 g, 14 mmol) and CsF (3.02 g, 20 mmol) in *N*,*N*-diethylaniline (24 ml) was refluxed for 4 h under argon with stirring. The mixture was diluted with ether. After removal of the insoluble material by filtration, the filtrate was washed with 5% hydrochloric acid and brine, and then dried over K_2CO_3. The residue in hexane was chromatographed on silica gel (No. 9385) with the same solvent to give **12** (2.18 g, 73%), bp 119—121 °C (10 mmHg) (lit.[13] bp 138—140 °C (15 mmHg)). ^{1}H-NMR (60 MHz): 2.45 (3H, s, Me),

6.36 (1H, m, C_3-H), 6.85—7.50 (3H, m, aromatic protons). MS *m/z*: 212 ($M^+ + 2$), 210 (M^+).

Oxidation of 7-Bromo-2-methylbenzo[*b*]furan (12) with RuO_4: 3-Bromo-2-hydroxybenzaldehyde (14) and 7-Bromo-2-hydroxy-2-methyl-2,3-dihydrobenzo[*b*]furan-3(2*H*)-one (15) A solution of $NaIO_4$ (4.05 g, 19.0 mmol) and $RuCl_3$ hydrate (0.025 g) in H_2O (12 ml) was added to a solution of **12** (1 g, 4.74 mmol) in CH_3CN (19 ml). The mixture was stirred under ice-cooling for 45 min and diluted with water, then extracted with CH_2Cl_2. A mixture of the residue in EtOH (120 ml) and 1% aqueous $NaHCO_3$ solution (60 ml) was stirred at 70 °C for 20 min under argon. The reaction mixture was poured into water, acidified with 10% hydrochloric acid, and then extracted with AcOEt. The residue in hexane–AcOEt (8 : 1) was subjected to flash chromatography on silica gel (No. 9385). Elution with the same solvent afforded **14** (0.40 g, 42%), mp 53—54 °C (lit.[14] 49 °C) (pale yellow needles from hexane). IR cm^{-1}: 1660 (C=O). ^{1}H-NMR (60 MHz): 6.94 (1H, t, J=7.6 Hz, C_5-H), 7.57 (1H, dd, J=7.6, 1.2 Hz, C_4-H), 7.81 (1H, dd, J=7.6, 1.2 Hz, C_6-H), 9.87 (1H, s, CHO), 11.6 (1H, s, OH). Elution with hexane–AcOEt (5 : 1) afforded **15** (156 mg, 14%), mp 88—89 °C (colorless needles from hexane–benzene). IR cm^{-1}: 3320 (OH), 1693 (C=O). ^{1}H-NMR (60 MHz): 1.69 (3H, s, Me), 4.60 (1H, br, OH), 6.96 (1H, t, J=7.6 Hz, C_5-H), 7.59 (1H, dd, J=7.6, 1.4 Hz, C_4-H or C_6-H), 7.82 (1H, dd, J=7.6, 1.4 Hz, C_6-H or C_4-H). MS *m/z*: 244 ($M^+ + 2$), 242 (M^+). *Anal.* Calcd for $C_9H_7BrO_3$: C, 44.47; H, 2.91. Found: C, 44.63; H, 2.81.

General Procedure for Oxidation of 2-Methylbenzofurans with Ozone The benzofuran (0.5 mmol) was dissolved in dry CH_2Cl_2 (25 ml) and cooled to −78 °C. Ozone was bubbled through the solution for 10—15 min with stirring. The pale-blue reaction mixture was stirred at −78 °C for 5 min. Excess ozone was removed by bubbling argon through the solution for about 10 min at −78 °C. Dimethyl sufide (2—5 ml) was added with stirring and the whole was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ether and the solution obtained was washed with water.

Salicylaldehyde (6) The residue obtained from ozonolysis of **5** was dissolved in $CHCl_3$–hexane (2 : 1) and subjected to chromatography on silica gel (No. 7734). Elution with the same solvent gave **6** (67%).

2-Acetoxy-1-naphthaldehyde (9) and 2-Hydroxy-1-naphthaldehyde (11) The residue obtained from ozonolysis of **8** was dissolved in CH_2Cl_2 and subjected to chromatography on silica gel (No. 7734). Elution with CH_2Cl_2 afforded **11** (5%), mp 80—84 °C (lit.[15] 80—81 °C) (colorless needles from hexane). Successive elution with the same solvent afforded **9**[10] (44%), mp 95—97 °C (colorless plates from hexane–AcOEt).

3-Bromo-2-hydroxybenzaldehyde (14) The residue obtained from ozonolysis of **12** was dissolved in EtOH (15 ml) and 1% aqueous $NaHCO_3$ solution (8 ml), and the solution was stirred at 70 °C for 0.5 h. The reaction mixture was poured into water, acidified with 10% hydrochloric acid, and then extracted with ether. The residue in AcOEt was subjected to chromatography on silica gel (No. 9385). Elution with hexane–AcOEt (12 : 1) gave **14**[14] (79%).

2-Hydroxy-3-methoxy-6-methylbenzaldehyde (21) The residue obtained from ozonolysis of **16** was dissolved in EtOH (15 ml) and 1% aqueous $NaHCO_3$ solution (8 ml). The mixture was refluxed for 5 h, poured into water, acidified with 5% hydrochloric acid, and then extracted with ether. Distillation of the residue under reduced pressure gave **21**[1] (86%), bp 90—100 °C (1 mmHg) (a yellow oil).

5-Formyl-6-hydroxy-7-methoxycoumarin (22) The residue obtained from ozonolysis of **17** was dissolved in EtOH (20 ml) and 1% aqueous $NaHCO_3$ solution (11 ml), and refluxed for 0.5 h. After cooling, the reaction mixture was poured into water, acidified with 5% hydrochloric acid, and then extracted with $CHCl_3$. The residue was recrystallized from AcOEt–EtOH to give **22**[5] (74%), mp 263—264 °C (pale yellow prisms).

6-(2-*N*-Carbobenzoxy-*N*-carbo-*tert*-butoxyaminoethyl)-2-hydroxy-3-methoxybenzaldehyde (23) The residue obtained from ozonolysis of **18** was dissolved in EtOH (20 ml) and 1% aqueous $NaHCO_3$ (11 ml). The mixture was refluxed for 0.5 h, poured into water, acidified with 5% hydrochloric acid and then extracted with ether. The residue in hexane–AcOEt (1 : 1) was subjected to chromatography on silica gel (No. 7734) with the same solvent to afford **23**[3] (71%), mp 69—70 °C (pale yellow prisms from AcOEt–hexane).

2-(2-Formyl-3-hydroxy-4-methoxyphenyl)-1-(*N*-methylformamido)-6,7-methylenedioxynaphthalene (24) The residue obtained from ozonolysis of **19** was dissolved in dioxane (16 ml) and 1% aqueous sodium hydroxide solution (8 ml) under ice-cooling. The mixture was stirred at room temperature for 2 h, poured into water, acidified with 5% hydrochloric acid, and then extracted with benzene. The residue in $CHCl_3$–AcOEt (20 : 1) was subjected to chromatography on silica gel (No. 7734) with the same solvent to afford **24**[2] (43%), mp 244—248 °C (pale yellow prisms from AcOEt–hexane).

2-Hydroxy-3,6-dimethoxybenzaldehyde (25) The residue obtained from ozonolysis of **20** was dissolved in EtOH (20 ml) and 1% aqueous $NaHCO_3$ solution (5 ml). The mixture was refluxed for 2 h, poured into water, acidified with 5% hydrochloric acid, and then extracted with CH_2Cl_2. The residue in benzene–$CHCl_3$ (4 : 1) was chromatographed on silica gel (No. 9385). Elution with the same solvent gave **25**[4] (61%), mp 69—71 °C (yellow plates from ether–hexane).

Oxidation of 7-Bromo-2-methylbenzo[*b*]furan (12) with OsO_4 OsO_4 (1 g, 3.93 mmol) was added to a solution of **12** (833 mg, 3.95 mmol) in dry pyridine (14 ml). After stirring at room temperature for 2 h, a solution of sodium hydrogen sulfite (1.64 g, 9.22 mmol) in water (24 ml) and pyridine (17 ml) was added. The reaction mixture was stirred at room temperature for a further 3 h, poured into water and then extracted with AcOEt. The extract was washed with 5% hydrochloric acid and brine. The residue was subjected to chromatography on silica gel (No. 9385). Elution with hexane gave the starting material (**12**) (58.6 mg, 7%). Elution with hexane–AcOEt (8 : 1) gave **14** (6.6 mg, 1%) and with hexane–AcOEt (6 : 1) gave **15** (672 mg, 70%).

Preparation of 3-Bromo-2-hydroxybenzaldehyde (14) from 15 Sodium borohydride (78.9 mg, 2.09 mmol) was added portionwise to a solution of **15** (502 mg, 2.06 mmol) in EtOH (40 ml) at room temperature. The reaction mixture was stirred for 10 min at the same temperature, then diluted with water, acidified with 10% hydrochloric acid, and extracted with AcOEt. The extract was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to afford a diastereomeric mixture of the dihydroxy phenol. MS *m/z*: 248 ($M^+ + 2$), 246 (M^+). The crude dihydroxyl phenol, without purification, was dissolved in MeOH (13 ml) and water (4.4 ml). Sodium periodate (699 mg, 3.28 mmol) was added to the solution and the whole was stirred at room temperature for 5 min, then poured into water (100 ml) and extracted with ether. The residue was recrystallized from hexane to afford **14**[14] (299 mg, 72%).

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References and Notes

1) H. Ishii, T. Ishikawa, S. Takeda, S. Ueki, and M. Suzuki, *Chem. Pharm. Bull.*, **40**, 1148 (1992).
2) H. Ishii, T. Ishikawa, S. Takeda, M. Suzuki, and T. Harayama, *Chem. Pharm. Bull.*, **40**, 2002 (1992).
3) H. Ishii, T. Ishikawa, S. Ohta, M. Suzuki, and T. Harayama, *Chem. Pharm. Bull.*, **40**, 1993 (1992).
4) H. Ishii, K. Kenmotsu, W. Döpke, and T. Harayama, *Chem. Pharm. Bull.*, **40**, 1770 (1992).
5) H. Ishii, T. Ishikawa, H. Wada, H. Miyazaki, Y. Kaneko, and T. Harayama, *Chem. Pharm. Bull.*, **40**, 2614 (1992).
6) P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
7) Interestingly, the ketone (**15**) did not undergo further oxidation upon re-treatment with RuO_4 under the same reaction conditions.
8) *a*) A. Mustafa, "Benzofurans," ed. by A. Weirsferger and E. C. Taylor, John Wiley and Sons, Inc., New York, 1974, pp. 59—61; *b*) A.v. Wacek, H. O. Eppinger, and A.v. Bézard, *Chem. Ber.*, **73**, 521 (1940); *c*) A. G. Schultz, J. J. Napier, and R. Ravichandran, *J. Org. Chem.*, **48**, 3408 (1983); *d*) J. M. McNamara and Y. Kishi, *Tetrahedron*, **40**, 4685 (1984).
9) In this case, **6** was obtained directly without hydrolyzing the oxidation product.
10) M. Eckstein, A. Kocwa, and H. Pazdro, *Roczniki Chem.*, **32**, 789 (1958) [*Chem. Abstr.*, **53**, 10198*a* (1959)].
11) *a*) The Aldrich Library of Infrared Spectra, p. 784; *b*) The Aldrich Library of NMR Spectra, Vol. VI, p. 65.
12) *a*) K. B. Sukumaran and R. G. Harvey, *J. Org. Chem.*, **45**, 4407 (1980); *b*) L. F. Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 430.
13) L. J. Powers, *J. Med. Chem.*, **19**, 57 (1976).
14) J. Müller, *Chem. Ber.*, **42**, 3695 (1909).
15) R. Adams and I. Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923).