(M^+, 72), 251 (57), 235 (83), 234 (46), 208 (39), 180 (100).

(c) With complex 25; 2-(methoxycarbonyl)-3,4,5-trimethoxybenzaldehyde: IR ($CHCl_3$) 1720, 1690, 1620 cm^{-1}; NMR ($CDCl_3$) 3.74 (3 H, s), 3.80 (3 H, s), 3.81 (3 H, s), 3.82 (3 H, s), 7.06 (1 H, s), 9.68 (1 H, s); MS, *m/e* (relative intensity) 254 (M^+, 29), 239 (26), 226 (59), 223 (38), 195 (100).

(d) With complex 26; 2-(methoxycarbonyl)-3-methoxyacetophenone: IR ($CHCl_3$) 1720, 1685, 1580 cm^{-1}; NMR ($CDCl_3$) 2.62 (3 H, s), 3.88 (3 H, s), 3.95 (3 H, s), 7.14 (1 H, m), 7.42 (2 H, m); MS, *m/e* (relative intensity) 208 (M^+, 11), 193 (100), 177 (38), 105 (20). **4-(Methoxycarbonyl)-3-methoxyacetophenone**: IR ($CHCl_3$) 1720, 1680, 1600, 885 cm^{-1}; NMR ($CDCl_3$) 2.64 (3 H, s), 3.92 (3 H, s), 3.96 (3 H, s), 7.52 (1 H, s), 7.50 (1 H, d, J = 7), 7.82 (1 H, d, J = 7); MS, *m/e* (relative intensity) 208 (M^+, 56), 193 (100), 177 (78), 165 (28), 133 (25).

Formylation of the Complexes 20 and 21. (a) With complex 21; 1,2,3,4-tetrahydro-1,7-dimethoxy-6-formylnaphthalene: IR (CCl_4) 1680, 1610 cm^{-1}; NMR (CCl_4) 3.40 (3 H, s), 3.84 (3 H, s), 4.16 (1 H, br s), 6.86 (1 H, s), 7.34 (1 H, s), 10.20 (1 H, s); MS, *m/e* (relative intensity) 220 (M^+, 13), 188 (100), 187 (23), 159 (23), 128 (21).

(b) With complex 20; 1,2,3,4-tetrahydro-2,2-dimethyl-1,7-dimethoxy-6-formylnaphthalene: IR ($CHCl_3$) 1680, 1610 cm^{-1}; NMR (CCl_4) 1.84 (3 H, s), 1.90 (3 H, s), 3.40 (3 H, s), 3.85 (3 H, s), 6.70 (1 H, s), 7.40 (1 H, s), 10.22 (1 H, s); MS, *m/e* (relative intensity) 248 (M^+, 13), 216 (59), 214 (32), 192 (100), 177 (41).

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Registry No. 1, 612-16-8; 2, 28281-58-5; 3, 57757-74-1; 4, 32820-10-3; 5, 85865-41-4; 6, 57757-81-0; 7, 85954-54-7; 8, 52520-37-3; 9, 85882-76-4; 10, 74411-87-3; 11, 85882-77-5; 12, 85882-78-6; 13, 74431-72-4; 14, 85882-79-7; 15, 85882-80-0; 16, 85882-81-1; 17, 74411-86-2; 18, 85922-59-4; 19, 85882-82-2; 20, 85882-83-3; 21, 85922-60-7; 22, 85893-28-3; 23, 71250-06-1; 24, 85893-29-4; 25, 85882-84-4; 26, 85882-85-5; 29, 76290-90-9; $Cr(CO)_6$, 13007-92-6; Me_3SiCl, 75-77-4; $ClCO_2Me$, 79-22-1; CO_2, 124-38-9; DMF, 68-12-2; 3-methoxy-4-(trimethylsilyl)benzyl alcohol, 85865-42-5; 3-(methoxymethoxy)-4-(methoxycarbonyl)benzyl alcohol, 85865-43-6; 3-(methoxymethoxy)-4-(trimethylsilyl)benzyl alcohol, 85865-44-7; 7-methoxy-6-(methoxycarbonyl)-1-tetralol, 76290-90-9; 7-methoxy-6-(trimethylsilyl)-1-tetralol, 76290-91-0; 7-methoxy-6-(1-hydroxy-4-methoxybenzyl)-1-tetralol, 76290-92-1; *p*-anisaldehyde, 123-11-5; dimethyl phthalate, 131-11-3; tigloyl chloride, 35660-94-7; 7-methoxy-6-[*o*-(methoxycarbonyl)-benzoyl]-1-tetralol, 76290-93-2; 7-methoxy-6-tigloyl-1-tetralol, 85865-45-8; 7-methoxy-2-methyl-6-(methoxycarbonyl)-1-tetralol, 76290-95-4; 7-methoxy-2-methyl-6-formyl-1-tetralol, 85865-46-9; 7-methoxy-2,2-dimethyl-6-formyl-1-tetralol, 85865-47-0; 2-(1-hydroxyethyl)-7-methoxy-6-(methoxycarbonyl)-1-tetralol, 76290-96-5; 2-(methoxycarbonyl)-3-methoxybenzyl methyl ether, 85865-48-1; 2,4-bis(methoxycarbonyl)-3-methoxybenzyl methyl ether, 85865-49-2; 3-methoxy-2-(methoxycarbonyl)benzaldehyde ethylene acetal, 85865-50-5; 2-(trimethylsilyl)-3-methoxybenzaldehyde ethylene acetal, 85865-51-6; 2,4-bis(trimethylsilyl)-3-methoxybenzaldehyde ethylene acetal, 85865-52-7; 2-(methoxycarbonyl)-3,4-dimethoxybenzaldehyde, 62059-59-0; 2,5-bis(methoxycarbonyl)-3,4-dimethoxybenzaldehyde, 85865-53-8; 2-(methoxycarbonyl)piperonal, 85865-54-9; 2,5-bis(methoxycarbonyl)piperonal, 85865-55-0; 2-(methoxycarbonyl)-3,4,5-trimethoxybenzaldehyde, 85865-56-1; 2-(methoxycarbonyl)-3-methoxyacetophenone, 85865-57-2; 4-(methoxycarbonyl)-3-methoxyacetophenone, 85865-58-3; 1,2,3,4-tetrahydro-1,7-dimethoxy-6-formylnaphthalene, 85865-59-4; 1,2,3,4-tetrahydro-2,2-dimethyl-1,7-dimethoxy-6-formylnaphthalene, 85865-60-7.

Supplementary Material Available: Three tables listing fractional coordinates, temperature factors, bond distances, and bond angles of complex 16 (5 pages). Ordering information is given on any current masthead page.

General Method for the Synthesis of Phthalaldehydic Acids and Phthalides from *o*-Bromobenzaldehydes via Ortho-Lithiated Aminoalkoxides

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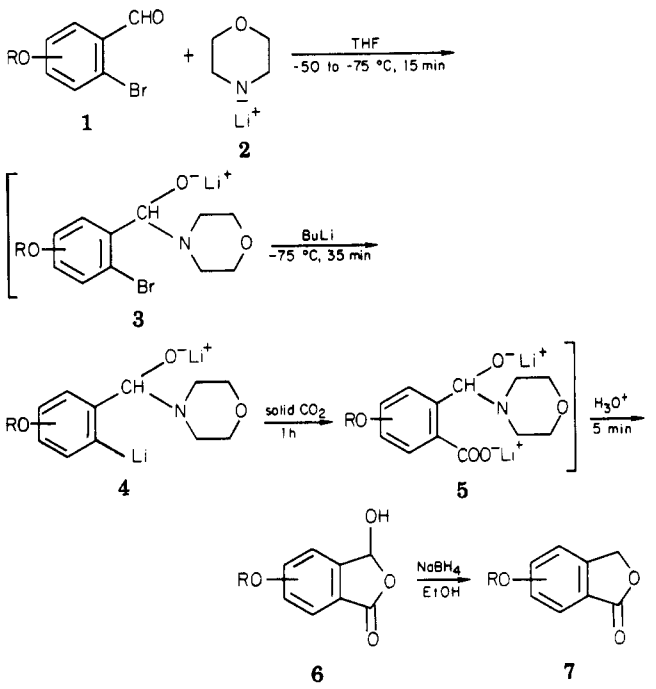
A general method for the synthesis of phthalaldehydic acids and phthalides, many of which are key intermediates in natural product synthesis, has been developed. *o*-Bromobenzaldehydes **1a–f** were first protected in situ as α-morpholinoalkoxides by reaction with lithium morpholide. Treatment of the α-morpholinoalkoxides **3a–f** with *n*-butyllithium (to exchange bromine with lithium) followed by sequential treatment with solid CO_2 and dilute acid afforded the phthalaldehydic acids **6a–f**, respectively. Reduction of **6a–f** with $NaBH_4$ in EtOH furnished the phthalides **7a–f**, respectively, in nearly quantitative yields. Efficient methods for the synthesis of the *o*-bromobenzaldehydes **1a–d**, which were not readily available, are also described.

Phthalaldehydic acids and phthalides are useful synthons for a number of classes of natural products. Phthalides have been used as key intermediates in the synthesis of functionalized naphthalenes and anthracenes, which in turn are used as synthons for tricyclic and tetracyclic linear aromatic natural products.[1,2] Phthalides have also been utilized in the synthesis of phthalide isoquinoline alkaloids,[1,3] some of which exhibit central nervous system activity.[3] Major methods for the synthesis of the more useful phthalides, namely, phthalides with alkoxy substituents on the benzene ring,[2] involve appropriate transformation of suitable ortho-lithiated benzyl alcohols,[3-6] *N,N*-dialkylbenzylamine,[3] or benzamides.[7]

(1) Snieckus, V. *Heterocycles* **1980**, 14, 1649–1676.
(2) (a) Franck, R. W.; John, T. V. *J. Org. Chem.* **1980**, *45*, 1170–1172. (b) Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. R. *Synthesis* **1980**, 72–74. (c) Larock, R. C.; Fellows, C. A. *J. Org. Chem.* **1980**, *45*, 363–365. (d) Kraus, G. A.; Pezzanite, J. O.; Sugimoto, H. *Tetrahedron Lett.* **1979**, 853–856. (e) Hauser, F. F.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178–180. (f) Broom, N. J. P.; Sammes, P. J. *J. Chem. Soc., Chem. Commun.* **1978** 162–164. (g) Larock, R. C. *Heterocycles* **1982**, *18*, 397–410.
(3) Hung, T. V.; Mooney, B. A.; Prager, R. H.; Tippett, J. M. *Aust. J. Chem.* **1981**, *34*, 383–394 and references cited therein.
(4) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835–1838.
(5) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195–1198.
(6) Noire, P. D.; Franck, R. W. *Synthesis* **1980**, 882–883.

0022-3263/83/1948-2356$01.50/0

Scheme I



Alternatively, alkoxy-substituted phthalides have been prepared by chloromethylation of alkoxybenzoic acids.[8]

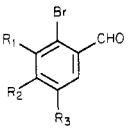
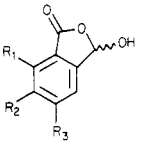
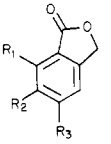
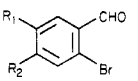
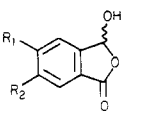
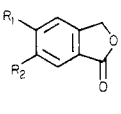
Phthalaldehydic acids have been of particular importance in the synthesis of zearalenone and its derivatives.[9] In spite of the general synthetic utility of phthalaldehydic acids, efficient methods for their synthesis are lacking. Phthalaldehydic acids have been synthesized from phthalides,[4] from phthalic anhydrides[10] in very poor yields, from benzamides,[7b] and from dimethyl acetals[11] and cyclohexylimines[12] of suitable benzaldehydes in modest overall yields via ortho metalation and carboxylation followed by hydrolysis.

In this paper we report a general and efficient method for the synthesis of a variety of phthalaldehydic acids in one step from *o*-bromobenzaldehydes based on the in situ method for protection of the aldehyde function recently reported by Comins and Brown.[13] The phthalaldehydic acids were then converted quantitatively to the corresponding phthalides.

Results and Discussion

Our basic strategy for the synthesis of phthalaldehydic acids was to introduce directly a carboxyl group ortho to the aldehyde function of the benzaldehyde. This was to be accomplished via the ortho-lithiated, in situ protected derivative of the benzaldehyde, thereby avoiding cumbersome protection and deprotection of the aldehyde function. Corresponding phthalides were then to be produced by reduction of the phthalaldehydic acids. This approach appeared simpler than the reverse process where the phthalide is synthesized first and is then converted to the phthalaldehydic acid.[4] For the synthesis of the phthalaldehydic acids, *o*-bromobenzaldehydes appeared to be suitable starting materials from the following considerations: (a) the aldehyde function of a benzaldehyde can be protected in situ[13] by reacting it with lithium morpholide (**2**) to give α-morpholino alkoxide (Scheme I), stable to organometallic reagents but readily hydrolyzed by aqueous acid; (b) metalation by lithium–bromine exchange,[14] rather than by lithium–hydrogen exchange,[15] should ensure specificity of metalation; (c) a variety of alkoxy-*o*-bromobenzaldehydes are available commercially or can be synthesized from readily available starting materials.

Table I. Phthalaldehydic Acids and Phthalides from *o*-Bromobenzaldehydes

bromo aldehyde	phthalaldehydic acid (% yield)	phthalide (% yield)[a,b]
		
1a, $R_1 = R_3 = OMe$; $R_2 = H$	**6a**, (74)	**7a**, (96)
b, $R_1 = R_3 = OCH_2Ph$; $R_2 = H$	**b** (70)	**b** (98)
c, $R_1 = R_2 = OMe$; $R_3 = H$	**c** (86)	**c** (94)
d, R_1 $R_2 = OCH_2O$; $R_3 = H$	**d** (88)	**d** (94)
		
1e, $R_1 = R_2 = OMe$	**6e** (82)	**7e** (95)
f, R_1,$R_2 = OCH_2O$	**f** (89)	**f** (93)

[a] Yields of isolated materials. [b] Based on phthalaldehydic acids.

After considerable experimentation, we established the following general procedure for the conversion of *o*-bromobenzaldehydes to phthalaldehydic acids (Scheme I and Table I). The aldehyde function of the *o*-bromobenzaldehyde **1** is protected in situ by reacting **1** at −50 °C with lithium morpholide (**2**) generated in situ in THF. *n*-Butyllithium in hexane is then added to exchange bromine with lithium, producing the ortho-lithiated morpholinoalkoxide **4**. This step is conducted for 35 min strictly at or below −75 °C to minimize side reactions. Addition of solid CO_2 followed by an acidic workup gave the phthalaldehydic acids **6a–f** (Table I). It was observed that the best results are obtained when only a slight excess (1.2 equiv/equiv of aldehyde) of lithium morpholide is used to protect the aldehyde function. In one run when 2 equiv of morpholide was used to protect 1 equiv of **1b** and 1 equiv of *n*-BuLi was used for the lithium–bromine exchange, 85% of the starting material was recovered unchanged. Temperatures higher than −75 °C for the lithium–bromine exchange step invariably led to side product formation which was most pronounced in the case of **1a** and **1b**.

Attempts to produce the ortho-lithiated morpholinoalkoxide **4** from **1c**, for example, by lithium–hydrogen exchange, rather than by lithium–bromine exchange as shown in Scheme I, with BuLi in Et_2O or THF (up to 25 °C, 4 h) were not successful. A mixture was formed as

(7) (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312. (b) DeSilva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099–5102.
(8) Bhattacharjee, D.; Popp, F. D. *J. Heterocycl. Chem.* **1980**, *17*, 315–320.
(9) Shipchandler, M. T. *Heterocycles* **1975**, *3*, 471–521.
(10) Taub, D.; Girotra, N. N.; Hoffsomer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443–2461.
(11) Plauman, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1979**, 4921–4924.
(12) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564–1566.
(13) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213–4216.
(14) Jones, R. G.; Gilman, H. *Org. React.* **1951**, *6*, 339–366.
(15) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1–360.

evidenced by TLC (silica gel, CH_2Cl_2) and the ^1H NMR spectrum of the product mixture obtained following methylation with dimethyl sulfate. Part of the problem may have been competitive, directed metalation arising from the methoxy groups as well as the morpholinoalkoxide group.[16]

As anticipated, the reduction of the phthalaldehydic acids **6a–f** with $NaBH_4$ in ethanol proceeded smoothly to give the phthalides **7a–f** in nearly quantitative yields.[17] The phthalaldehydic acids **6** and the phthalides **7** were characterized by IR and NMR techniques. In addition, the physical properties of the known compounds were in complete agreement with those reported in the literature (see Experimental Section). Both IR and NMR data indicate that in acetone or chloroform **6a–f** exist almost exclusively in the lactol forms as shown.

Some of the more important features of the present method can be summarized as follows (see Table I): (a) the method is applicable to benzyloxy derivatives; (b) even when excellent alternate metalation sites are present (especially position 4 in **1a** and **1b**), the phthalaldehydic acids are obtained in very good yields; (c) the method allows for the separate synthesis of isomeric pairs such as **6c,e**, **6d,f**, **7c,e**, and **7d,f**.

The present method complements the synthesis of phthalaldehydic acids and phthalides via ortho-lithiated *N,N*-diethylbenzamides[7] where the aldehyde function is introduced ortho to the derivatized carboxyl group as opposed to the introduction of the carboxyl group ortho to the derivatized aldehyde function in the present method. The principal advantage of the benzamide method over the present method, where comparisons can be made, is that the ortho-lithiated dialkylbenzamides are readily produced under very mild conditions by the lithium–hydrogen exchange of the corresponding dialkylbenzamides[7] whereas the generation of the ortho-lithiated benzylmorpholinoalkoxides (cf. **4**) under comparable conditions require the presence of a bromo group ortho to the aldehyde function. The principal disadvantage of the benzamide method for the synthesis of phthalaldehydic acids[7b] is that the carboxyl group is generated from the tertiary amide function which is notable[7] for its resistance to hydrolysis.

One key factor in the development of the present method for the synthesis of phthalaldehydic acids and phthalides was the availability of the appropriate *o*-bromobenzaldehydes. We have developed convenient methods for the synthesis of those bromoaldehydes which are not commercially available. 2-Bromo-3,5-dimethoxybenzaldehyde (**1a**) and 2-bromo-3,5-bis(benzyloxy)benzaldehyde (**1b**) were synthesized from 3,5-dimethoxybenzyl alcohol (**8a**) and 3,5-bis(benzyloxy)benzyl alcohol (**8b**), respectively, by quantitative and regioselective bromination[6] with *N*-bromosuccinimide followed by quantitative oxidation with pyridinium chlorochromate. Both 2-bromo-3,4-dimethoxybenzaldehyde (**1c**) and 2-bromo-3,4-(methylenedioxy)benzaldehyde (**1d**) were produced in good yields from readily available isovanillin (**10**). Selective bromination of **10** was achieved by a modification of the literature procedure,[18,19] to give 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**11**) in 70–75% yield. Direct methylation of **11** gave **1c**, whereas its demethylation with $AlCl_3$/pyridine/CH_2Cl_2[20] followed by methylenation[21] by reaction with CH_2Br_2 in DMF in the presence of anhydrous KF gave **1d**.

Experimental Section

General Methods. Infrared spectra were determined on a Beckman IR-33 spectrophotometer and are reported in reciprocal centimeters. ^1H NMR spectra were determined in the indicated solvent on a Varian T-60 spectrometer, and chemical shifts are reported in δ units downfield from internal Me_4Si. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. THF (Fischer, containing 0.02% water) was dried for at least 24 h over 3-Å molecular sieves before use. Morpholine (Fischer) was stored over NaOH pellets under nitrogen in a septum-capped bottle for at least 24 h before use.

Phthalaldehydic Acids 6a–f from *o*-Bromobenzaldehydes 1a–f. General Procedure. A 100-mL, three-necked, round-bottomed flask equipped with a stirring bar, septum cap, dropping funnel, nitrogen inlet, and thermometer was flame-dried under a stream of dry nitrogen and then cooled to room temperature. Morpholine (1.05 g, 12 mmol) and THF (20 mL) were placed in the flask, and a solution of the bromoaldehyde (**1**, 10 mmol) in 20 mL of THF was placed in the dropping funnel. The mixture in the flask was cooled with stirring to −40 to −50 °C in a dry ice–acetone bath, and *n*-butyllithium (1.6 M in hexane, 7.5 mL, 12 mmol) was added all at once. After 5 min, the solution of the aldehyde was added from the dropping funnel over a period of 1 min, and the resulting mixture was cooled to −75 °C over 15 min. *n*-Butyllithium (1.6 M in hexane, 10 mL, 16 mmol) was then added dropwise, keeping the temperature at or below −75 °C. After the addition was over (~5 min), the mixture was stirred at −75 °C for 35 min, and then a large excess of solid CO_2 was introduced. After 1 h, the mixture was allowed to attain room temperature and was acidified to pH ~1 with 6 N HCl. The solution after dilution with brine was extracted with Et_2O (4 × 30 mL) and then exhaustively with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to dryness to give the crude phthalaldehydic acids **6**. Methods of purification and physical properties of **6a–f** are described under individual headings below.

5,7-Dimethoxyphthalaldehydic Acid (6a). The crude product (1.82 g, 86%) was recrystallized from EtOAc–hexane to give 1.6 g (74%) of product: mp 186–189 °C (lit.[10] mp 184–189 °C; lit.[4] mp 183–189 °C); IR (Nujol), 3400, 1755, 1605 cm^{-1}; ^1H NMR (acetone-d_6) δ 2.80 (br s, 1 H, OH), 3.96 (s, 6 H, OMe), 6.45 (br, s, 1 H, CHOH), 6.66 (d, $J_{4,6}$ = 2 Hz, 1 H, H-4 or H-6), 6.73 (d, $J_{4,6}$ = 2 Hz, 1 H, H-4 or H-6).

5,7-Bis(benzyloxy)phthalaldehydic Acid (6b). The light pink crude product (3.6 g) was chromatographed on a column of silica gel (25 g) in CH_2Cl_2. Elution with CH_2Cl_2 removed all the nonpolar impurities. Further elution with 25% Et_2O in CH_2Cl_2 followed by evaporation of solvent gave essentially pure **6b**, which was recrystallized from EtOAc–hexane to give 2.54 g (70%) of product: mp 126–129 °C; IR (Nujol) 3390, 1750, 1615, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.95 (s, 2 H, OCH_2Ph), 5.10 (s, 2 H, OCH_2Ph), 5.80 (br s, 1 H, OH), 6.44 (d, $J_{4,6}$ = 2 Hz, 1 H, H-4 or H-6), 6.48 (s, 1 H, CHOH), 6.65 (d, $J_{4,6}$ = 2 Hz, 1 H, H-4 or H-6), 7.17–7.50 (m, 10 H, Ph). Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.92; H, 5.01. Found: C, 72.60; H, 5.12.

6,7-Dimethoxyphthalaldehydic Acid (6c). The crude product was recrystallized from H_2O to give 1.8 g (86%) of **6c**: mp 142–145 °C; IR (Nujol) 3440, 1760, 1600 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.94 (s, 6 H, OMe), 6.53 (br s, 1 H, CHOH), 7.37 (br s, 2 H, H-4 and H-5). Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.00; H, 5.09.

(16) After the submission of the present work for publication, a report appeared (Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979–3982) describing the directed ortho lithiation of α-(*N*-methylpiperazino)benzyl alkoxides, derived in situ from benzaldehydes, by using BuLi in refluxing benzene.

(17) It should be noted that a more direct route to phthalide **7a** has been reported and involved lithiation followed by carboxylation of 3,5-dimethoxybenzyl alcohol (**8a**).[4-6] Noire and Franck[6] and Uemura and co-workers[5] report formation of **7a** in 8% and 9% yields, respectively, together with two other compounds in higher yields than **7a**. In contrast, Trost and co-workers[4] reported quantitative yields of **7a** (based on 37% recovered **8a**). These differences may be due to the solvent used by the investigators.

(18) Lock, G. *Monatsh. Chem.* **1934**, *64*, 341–348.

(19) Henry, T. A.; Sharp, T. M. *J. Chem. Soc.* **1930**, 2279–2285.

(20) Lange, R. G. *J. Org. Chem.* **1962**, *27*, 2037–2039.

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6,7-(Methylenedioxy)phthalaldehydic Acid (6d). The crude product obtained from 850 mg (3.71 mmol) of **1d** was recrystallized from H_2O to give 634 mg (88%) of **6d**: mp 153–155 °C (lit.[12] mp 164.5–165.5 °C, lit.[22] mp 155 °C); IR (Nujol) 3400, 1765, 1580 cm^{-1}; ^1H NMR (acetone-d_6) δ 5.80 (br s, 1 H, CHOH), 6.27 (s, 2 H, OCH_2O), 7.20 (br s, 2 H, H-4 and H-5).

5,6-Dimethoxyphthalaldehydic Acid (6e). Recrystallization of the crude product (1.9 g) from EtOAc gave 1.72 g (82%) of **6e** as an amorphous solid: mp 173–176 °C; IR (Nujol) 3280, 1740, 1605 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.30 (br, 1 H, OH), 3.93 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 6.50 (br, 1 H, CHOH), 7.20 (s, 1 H, H-4), 7.25 (s, 1 H, H-7). Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 56.84; H, 4.92.

5,6-(Methylenedioxy)phthalaldehydic Acid (6f). The crude product (2 g) on recrystallization from H_2O gave 1.72 g (89%) of **6f**: mp 165–167 °C (lit.[12] mp 165–165.5 °C, lit.[22] mp 167 °C); IR (Nujol) 3280, 1720, 1605 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.13 (br s, 1 H, OH), 6.20 (s, 2 H, OCH_2O), 6.57 (br s, 1 H CHOH), 7.05 (s, 1 H, H-4), 7.10 (s, 1 H, H-7).

Preparation of 1(3*H*)-Isobenzofuranones (Phthalides) 7a–f from Phthalaldehydic Acids 6a–f. General Procedure. To a stirred solution or suspension of the phthalaldehydic acid **6** (2 mmol) in 15 mL of EtOH at 0–5 °C was added $NaBH_4$ (305 mg, 8 mmol) in three or four portions. The mixture was stirred at 0–5 °C for 2 h and then at 25 °C for 12 h. Excess $NaBH_4$ was destroyed by the careful addition of dilute HCl and then the mixture was evaporated in vacuo to dryness. The residue was treated with 5 mL of 6 N HCl, diluted with brine, and then exhaustively extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with brine, dried (Na_2SO_4), and then evaporated in vacuo to dryness to give essentially pure phthalide **7** in nearly quantitative yields (see Table I). Physical properties of the individual phthalides are described below.

5,7-Dimethoxyisobenzofuran-1(3*H*)-one (5,7-dimethoxyphthalide, 7a): recrystallized from acetone–hexane; mp 148–150 °C (lit.[4] mp 146–148 °C, lit.[6] mp 151–152 °C); IR (Nujol) 1755, 1605 cm^{-1} ^1H NMR ($CDCl_3$) δ 3.91 (s, 3 H, OMe), 3.97 (s, 3 H, OMe), 5.17 (s, 2 H, H-3), 6.40–6.57 (m, 2 H, H-4 and H-6).

5,7-Bis(benzyloxy)isobenzofuran-1(3*H*)-one (5,7-bis(benzyloxy)phthalide, 7b): recrystallized from CH_2Cl_2–hexane; mp 210–213 °C; IR ($CHCl_3$) 1750, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.10 (s, 2 H, OCH_2Ph), 5.18 (s, 2 H, OCH_2Ph), 5.29 (s, 2 H, H-3), 6.56 (s, 2 H, H-4 and H-6), 7.33–7.57 (m, 10 H, Ph). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 75.90; H, 5.31.

6,7-Dimethoxyisobenzofuran-1(3*H*)-one (6,7-dimethoxyphthalide, 7c): recrystallized from EtOAc–hexane: mp 97–100 °C (lit.[3] mp 97–100 °C, lit.[23] mp 101–102 °C); IR (Nujol) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 5.23 (s, 2 H, H-3), 7.23 (d, $J_{4,5}$ = 8 Hz, 1 H), 7.47 (d, $J_{4,5}$ = 8 Hz, 1 H).

6,7-(Methylenedioxy)isobenzofuran-1(3*H*)-one (6,7-(methylenedioxy)phthalide, 7d): recrystallized from EtOAc–hexane; mp 233–235 °C) (lit.[3] mp 236–238 °C, lit.[24] mp 226 °C; IR (Nujol) 1750 cm^{-1}; ^1H NMR (acetone-d_6) δ 5.32 (s, 2 H, H-3), 6.23 (s, 2 H, OCH_2O), 7.07 (d, $J_{4,5}$ = 7.8 Hz, 1 H), 7.23 (d, $J_{4,5}$ = 7.8 Hz, 1 H).

5,6-Dimethoxyisobenzofuran-1(3*H*)-one (5,6-dimethoxyphthalide, 7e): recrystallized from EtOAc–hexane: mp 155–157 °C; IR (Nujol) 1750, 1605 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.92 (s, 6 H, OMe), 5.21 (s, 2 H, H-3), 7.15 (s, 1 H, H-4), 7.21 (s, 1 H, H-7). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.77; H, 5.45.

5,6-(Methylenedioxy)isobenzofuran-1(3*H*)-one (5,6-(methylenedioxy)phthalide, 7f): recrystallized from $CHCl_3$–hexane; mp 188–190 °C; IR (Nujol) 1745 cm^{-1}; ^1H NMR (acetone-d_6) δ 5.24 (s, 2 H, H-3), 6.21 (s, 2 H, OCH_2O), 7.09 (s, 1 H, H-4), 7.15 (s, 1 H, H-7). Anal. Calcd for $C_9H_6O_4$: C, 60.68; H, 3.39. Found: C, 60.96; H, 3.33.

2-Bromo-3,5-dimethoxybenzyl alcohol (9a) was prepared by the NBS bromination of 3,5-dimethoxybenzyl alcohol (**8a**) as described by Noire and Franck;[6] mp 95–96 °C (lit.[6] mp 95–96 °C.

2-Bromo-3,5-dimethoxybenzaldehyde (1a). To a mechanically stirred suspension of pyridinium chlorochromate (8.6 g, 40 mmol) in 20 mL of CH_2Cl_2 was added a solution of 2-bromo-3,5-dimethoxybenzyl alcohol (**9a**; 4.94 g, 20 mmol) in 30 mL of CH_2Cl_2 all at once at 25 °C. After the mixture was stirred at 25 °C for 1.75 h, the supernatant was decanted, and the black gummy residue was washed thoroughly with CH_2Cl_2 (3 × 20 mL). The combined organic layers were diluted with Et_2O (10–15% of the total volume of CH_2Cl_2) and then passed through a column of silica gel (20 g) in 9:1 CH_2Cl_2/Et_2O. Further elution with 15% Et_2O in CH_2Cl_2 and evaporation of combined eluents gave 4.8 g (98%) of **1a** as a pale yellow solid which was recrystallized from acetone–hexane to give 4.7 g of **1a**: mp 115–116 °C; IR (Nujol) 1680, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 6.67 (d, $J_{4,6}$ = 3.2 Hz, 1 H, H-4), 7.02 (d, $J_{6,4}$ = 3.2 Hz, 1 H, H-6), 10.37 (s, 1 H, CHO). Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 44.18; H, 3.75.

2-Bromo-3,5-bis(benzyloxy)benzyl Alcohol (9b). 3,5-Bis(benzyloxy)benzyl alcohol[25] (**8b**; 32 g, 100 mmol) was dissolved in 500 mL of CCl_4 by being warmed and then was cooled to 25 °C. NBS (freshly recrystallized from H_2O and dried over P_2O_5 under vacuum; 17.8 g, 100 mmol) was then added with stirring in portions over a period of 5 min. The mixture was then refluxed gently for 40 min, cooled to 25 °C, and diluted with CH_2Cl_2 to produce a clear solution. The solution was carefully washed with 1 N NaOH (200 mL), H_2O (until the aqueous layer was neutral), and brine, dried (Na_2SO_4), and then evaporated in vacuo to dryness to give 39.2 g (98.3%) of **9b**: homogeneous by TLC (10% Et_2O in CH_2Cl_2) R_f 0.4; mp 108–110 °C; ^1H NMR ($CDCl_3$) δ 2.05 (s, 1 H, OH), 4.70 (s, 2 H, CH_2OH), 5.00 (s, 2 H OCH_2Ph), 5.07 (s, 2 H, OCH_2Ph), 6.52 (d, $J_{4,6}$ = 3 Hz, 1 H, H-4 or H-6), 6.78 (d, $J_{4,6}$ = 3 Hz, 1 H, H-4 or H-6), 7.28–7.50 (m, 10 H, Ph). Anal. Calcd for $C_{21}H_{19}BrO_3$: C, 63.17; H, 4.78. Found: C, 62.90; H, 5.09.

2-Bromo-3,5-bis(benzyloxy)benzaldehyde (1b). 2-Bromo-3,5-bis(benzyloxy)benzyl alcohol (**9b**; 39.1 g, 98 mmol) in 200 mL of CH_2Cl_2 was oxidized with 42.14 g (196 mmol) of pyridinium chlorochromate in 100 mL of CH_2Cl_2 in the same manner as described above for the synthesis of **1a**. The crude product was recrystallized from acetone–ethanol (95:5) to give 37.74 g (97%) of **1b**: mp 124–126 °C; IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.06 (s, 2 H, OCH_2Ph), 5.13 (s, 2 H, OCH_2Ph), 6.82 (d, $J_{4,6}$ = 3.2 Hz, 1 H, H-4), 7.13 (d, $J_{6,4}$ = 3.2 Hz, 1 H, H-6), 7.33–7.52 (m, 10 H, Ph), 10.38 (s, 1 H, CHO). Anal. Calcd for $C_{21}H_{17}BrO_3$: C, 63.49; H, 4.31. Found: C, 63.10; H, 4.51.

2-Bromo-3-hydroxy-4-methoxybenzaldehyde (11). Isovanillin (**10**; 38 g, 250 mmol) was dissolved in 300 mL of glacial AcOH by warming the mixture. A solution of Br_2 (40 g, 250 mmol) in 40 mL of glacial AcOH was added dropwise with vigorous stirring at 20–25 °C over a period of 35 min. After the mixture had been stirred for 1.5 h at 20–25 °C, 500 mL of ice-cold H_2O was added, and the mixture was stirred for a further 30 min and then filtered. The precipitate was washed with ice-cold H_2O (4 × 200 mL) and dried over P_2O_5 to give **11**: 40.5 g (70%); mp 202–206 °C. One recrystallization from absolute EtOH raised the melting point to 208–211 °C (lit.[18] mp 210 °C): IR (Nujol) 3170, 1668 cm^{-1}; ^1H NMR (acetone-d_6) δ 4.02 (s, 3 H, OMe), 7.13 (d, $J_{5,6}$ = 8.5 Hz, 1 H, H-5), 7.52 (d, $J_{5,6}$ = 8.5 Hz, 1 H, H-6), 8.62 (s, 1 H, OH), 10.18 (s, 1 H, CHO).

2-Bromo-3,4-dimethoxybenzaldehyde (1c). 2-Bromo-3-hydroxy-4-methoxybenzaldehyde (**11**; 9.2 g, 40 mmol) was dissolved in a solution of 4.1 g of KOH (64 mmol) in 50 mL of H_2O. To the bright yellow solution of 50 °C was added with vigorous stirring 8.2 g (64 mmol) of dimethyl sulfate dropwise over a period of 10 min. After being stirred for an additional 15 min, the pale yellow mixture containing the solid product was cooled and filtered. The precipitate was washed twice with 1 N NaOH and then with H_2O. The white solid was dissolved in CH_2Cl_2, and the resulting solution was washed with brine, dried (Na_2SO_4), and then evaporated in vacuo to dryness to give 9.6 g (96%) of **1c**: mp 83–84 °C (lit.[18] mp 80 °C); IR (Nujol) 1683 cm^{-1}; ^1H NMR $CDCl_3$) δ 3.90 (s, 3 H, OMe), 3.98 (s, 3 H, OMe), 6.98 (d, $J_{5,6}$ = 9 Hz, 1 H, H-5), 7.74 (d, $J_{5,6}$ = 9 Hz, 1 H, H-6), 10.23 (s, 1 H, CHO).

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2-Bromo-3,4-dihydroxybenzaldehyde (12). To a stirred suspension of 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**11**; 11.55 g, 50 mmol) in 200 mL of dry CH_2Cl_2 (dried by storing analytical reagent CH_2Cl_2, Fisher, over 3-Å molecular sieves) under an N_2 atmosphere was added anhydrous $AlCl_3$ (7.35 g, 55 mmol) gradually over a period of 5 min. Anhydrous pyridine (freshly distilled after being stored over NaOH pellets; 17.4 g, 17.72 mL, 220 mmol) was then added dropwise to the vigorously stirred mixture. The clear, homogeneous, orange solution was then refluxed under N_2 for 30 h. After cooling, the mixture was acidified to pH ~1 with 6 N HCl and filtered. The precipitate was mostly the product and was dissolved in a minimum volume of acetone. The aqueous layer of the filtrate was separated (from the organic layer which contained traces of starting material and was discarded) and extracted twice with Et_2O. The Et_2O extracts were combined with the acetone solution of the precipitate, and the resulting mixture was diluted with 400 mL of Et_2O, washed with brine (3 × 50 mL), dried (Na_2SO_4), and then evaporated in vacuo to dryness to give **12**: 10.42 g (96%); mp 179–181 °C dec. An analytical sample was prepared by recrystallization from EtOAc–hexane: mp 181–183 °C dec; IR (Nujol) 3400, 1665, 1568 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.00 (d, $J_{5,6}$ = 8.2 Hz, 1 H, H-5), 7.42 (d, $J_{5,6}$ = 8.2 Hz, 1 H, H-6), 8.55 (br, s, 2 H, OH), 10.20 (s, 1 H, CHO). Anal. Calcd for $C_7H_5BrO_3$: C, 38.74; H, 2.50. Found: C, 38.85; H, 2.50.

2-Bromo-3,4-(methylenedioxy)benzaldehyde (1d). To a stirred solution of 2-bromo-3,4-dihydroxybenzaldehyde (**12**; 5.43 g, 25 mmol) in 75 mL of dry DMF under N_2 atmosphere was added anhydrous KF (PCR Inc., anhydrous material freshly dried at 0.05 mm over P_2O_5 for 24 h, 7.25 g, 125 mmol). After 15 min, CH_2Br_2 (4.79 g, 1.93 mL, 27.5 mmol) was added, and the mixture was heated at 115 °C with stirring for 2 h. The mixture was then evaporated in vacuo to dryness, and the residue was placed on a sintered-glass funnel and washed exhaustively with Et_2O. The combined Et_2O solutions were washed with water and brine, dried (Na_2SO_4), and then evaporated in vacuo to dryness to give **1d**: 4.87 g (86%); mp 129–133 °C. An analytical sample was prepared by recrystallization from benzene–hexane: mp 131–133 °C; IR (Nujol) 1685, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.17 (s, 2 H, OCH_2O), 6.86 (d, $J_{5,6}$ = 8.2 Hz, 1 H, H-5), 7.57 (d, $J_{5,6}$ = 8.2 Hz, 1 H, H-6), 10.17 (s, 1 H, CHO). Anal. Calcd for $C_8H_5BrO_3$: C, 41.95; H, 2.20. Found: C, 42.28; H, 2.19.

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Registry No. **1a**, 85565-93-1; **1b**, 85565-94-2; **1c**, 55171-60-3; **1d**, 56008-63-0; **1e**, 5392-10-9; **1f**, 15930-53-7; **6a**, 85925-67-3; **6b**, 85925-68-4; **6c**, 479-87-8; **6d**, 77632-09-8; **6e**, 77619-89-7; **6f**, 62869-57-2; **7a**, 3465-69-8; **7b**, 85925-69-5; **7c**, 569-31-3; **7d**, 4741-65-5; **7e**, 531-88-4; **7f**, 4792-36-3; **8a**, 705-76-0; **8b**, 24131-31-5; **9a**, 74726-76-4; **9b**, 67093-26-9; **10**, 621-59-0; 11, 2973-58-2; **12**, 4815-97-8; morpholine, 110-91-8.

Synthesis of the Isomeric Phenols and the *trans*-2,3-Dihydrodiol of Fluoranthene

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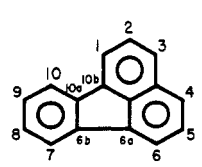
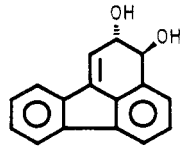
The syntheses of 1-hydroxy-, 2-hydroxy-, 7-hydroxy-, and 8-hydroxyfluoranthene, as well as that of *trans*-2,3-dihydroxy-2,3-dihydrofluoranthene, are described. UV and fluorescence spectra are reported for all five isomeric fluoranthenols as well as for the *trans*-2,3-dihydrodiol.

Fluoranthene (1) is one of the more prevalent polycyclic aromatic hydrocarbons (PAH) in the human environment. Fluoranthene and its methylated derivatives are formed by incomplete combustion of organic matter and are found in cigarette smoke, air pollution, coal tar, surface water, and soil.[1-3] Fluoranthene and several of its methylated derivatives are mutagenic in the Ames test.[4,5] The major mutagenic metabolite of 1 has been identified as *trans*-



1



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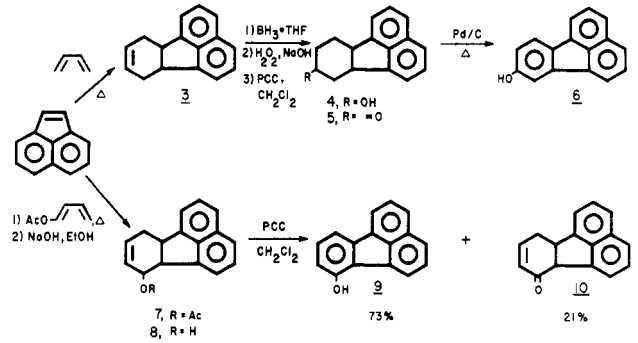
2,3-dihydroxy-2,3-dihydrofluoranthene (**2**).[5] Although fluoranthene is not active as a tumor initiator or complete carcinogen, this PAH is a potent cocarcinogen on mouse skin when applied together with benzo[*a*]pyrene.[6] 2-Methyl- and 3-methylfluoranthene have been shown to be active as tumor initiators.[1]

Our studies on the metabolism of fluoranthene and alkylfluoranthenes required UV spectra of synthetic reference standards of all the phenols of fluoranthene and its

Scheme I. Synthesis of 7- and 8-Hydroxyfluoranthene



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