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Aromatic Hydroxylation. Hydroxybenzaldehydes from Bromobenzaldehydes via Reaction of in Situ Generated, Lithiated α-Morpholinobenzyl Alkoxides with Nitrobenzene

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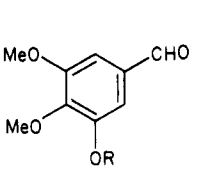
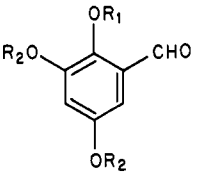
A general method for the one-step conversion of bromobenzaldehydes to the corresponding hydroxybenzaldehydes has been developed. The method involves in situ protection of the aldehyde function of the bromobenzaldehyde as its lithium morpholinoalkoxide, followed by lithium–bromine exchange, reaction with nitrobenzene at −75 °C, and a subsequent acidic workup. The method has been applied to the synthesis of 4,5-dimethoxy-3-hydroxy- (**1a**), 3,5-dimethoxy-2-hydroxy- (**2a**), 3,5-bis(benzyloxy)-2-hydroxy- (**2b**), 3,4-dimethoxy-2-hydroxy- (**14**), 3-hydroxy-4,5-(methylenedioxy)- (**16**), and 4,5-dimethoxy-2-hydroxybenzaldehydes (**18**) from the bromobenzaldehydes **4**, **12a**, **12b**, **13**, **15**, and **17**, respectively.

Hydroxybenzaldehydes are very rarely synthesized by the direct introduction of a hydroxyl group into the corresponding benzaldehydes, the reason being that very few of the existing methods[1-3] of aromatic hydroxylation are applicable[1-2,4-6] to benzaldehydes, and the methods that are applicable often suffer from the lack of generality, low yield, multistep sequence, and overoxidation problems. Another reason is that a variety of hydroxybenzaldehydes are readily prepared by the formylation of the corresponding phenols,[1,7] by the selective dealkylation of alkoxybenzaldehydes,[1,8] by the selective alkylation of polyhydroxybenzaldehydes,[8] or by the transformation of other hydroxybenzene derivatives to hydroxybenzaldehydes.[2] Nonetheless, quite frequently occasions arise when a hydroxybenzaldehyde is best synthesized by the introduction of a hydroxyl group into a specific position of the benzaldehyde. Three such examples are the hydroxybenzaldehydes **1a**, **2a**, and **2b**.

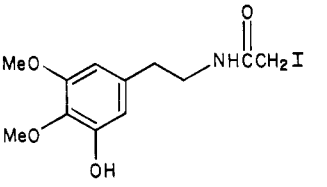
We needed **1a** (as its *O*-benzyl ether **1b**) for the synthesis of the phenylethylamine derivative **3**, as an affinity labeling



1a, R = H
b, R = CH_2Ph



2a, R_1 = H; R_2 = Me
b, R_1 = H; R_2 = CH_2Ph
c, R_1 = R_2 = Me
d, R_1 = R_2 = CH_2Ph



3

reagent[9] for the enzyme catechol *O*-methyltransferase. Hydroxybenzaldehyde **1a**, which is also a component of a number of important alkaloids,[10] is inaccessible by the earlier methods[11,12] which involved synthesis from 3,4,5-

(1) Wedemeyer, K.-F. In "Methoden der Organischen Chemie—Phenole"; Müller, E., Ed.; Georg Thieme Verlag, Stuttgart, 1976; Vol. VI/1c.
(2) (a) Harrison, I. T.; Harrison, S. "Compendium of Organic Synthetic Methods"; Wiley: New York, 1971, Vol. I; 1974, Vol. II. (b) Hegedus, L. S.; Wade, Jr., L. *Ibid.* **1977**, Vol. III. (c) Wade L. G., Jr. *Ibid.* 1980, Vol. IV.
(3) Dolson, M. G.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 2361–2371 and references cited therein.
(4) "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, pp 453–455.
(5) Banerjee, S. K.; Manolopoulo, M.; Pepper, J. M. *Can. J. Chem.* **1962**, *40*, 2175–2177.
(6) Jacob, P., III; Shulgin, A. T. *Synth. Commun.* **1981**, *11*, 969–977.
(7) Olah, G. A.; Kuhn, S. J. In "Friedel-Crafts and Related Reactions"; Olah, G. A.; Ed.; Wiley Interscience: New York, 1964; Vol. III, pp 1153–1256.
(8) (a) Haslam, E. In "Protective Groups in Organic Chemistry"; McOmie, J. F. W., Ed.; Plenum: New York, 1973; Chapter 4. (b) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981; Chapter 3.
(9) Borchardt, R. T.; Thakker, D. R. *Methods Enzymol.* **1977**, *46*, 554–561.
(10) (a) Wagner, H. *Recent Adv. Phytochem.* **1979**, *12*, 589–616. (b) Kametani, T. In "The Total Synthesis of Natural Products"; Apsimon, J., Ed.; Wiley: New York, 1977; Vol. 3, Chapter 1.
(11) Mauthner, F. *Ann. Chem.* **1926**, *449*, 102–108.

0022-3263/83/1948-1941$01.50/0

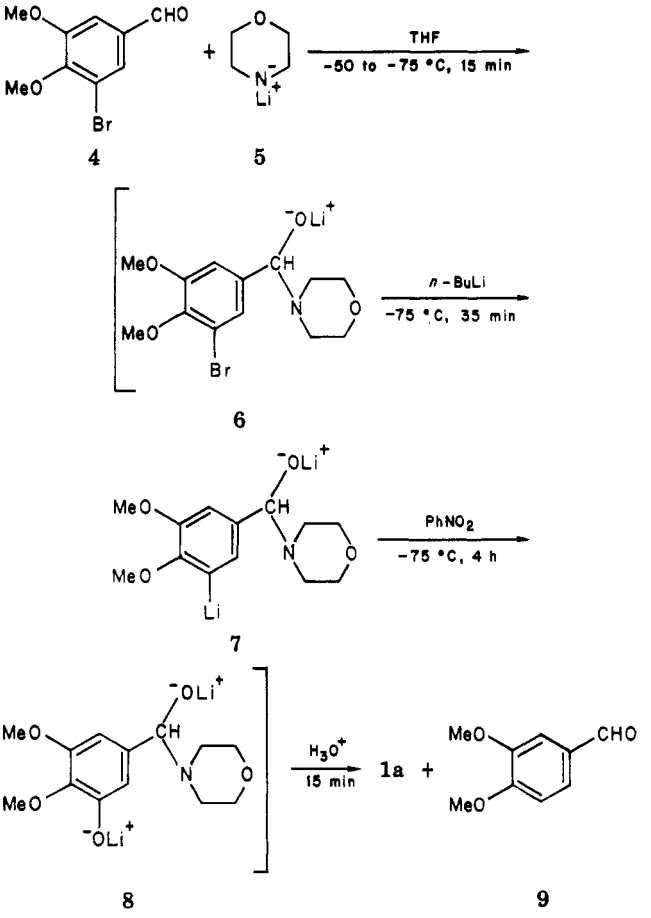
trihydroxybenzoic acid by selective O-methylation followed by conversion of the carboxyl group to the aldehyde. More recently[6] **1a** has been synthesized by a four-step hydroxylation of the corresponding bromobenzaldehyde **4**. The hydroxybenzaldehydes **2a** (as its *O*-methyl ether **2c**) and **2b** (as its *O*-benzyl ether **2d**) were required for the synthesis of 4,5,7-trihydroxytryptamine, an analogue of the pharmacologically important serotonin neurotoxin 5,7-dihydroxytryptamine.[13] Although use of the hydroxybenzaldehyde **2a** has been indicated,[14] no details of its synthesis were given. Hydroxybenzaldehyde **2b** and its *O*-benzyl derivative **2d** have not been described in the literature. We now report a hydroxylation procedure that allows one-step conversion of bromobenzaldehydes to the corresponding hydroxybenzaldehydes.

Results and Discussion

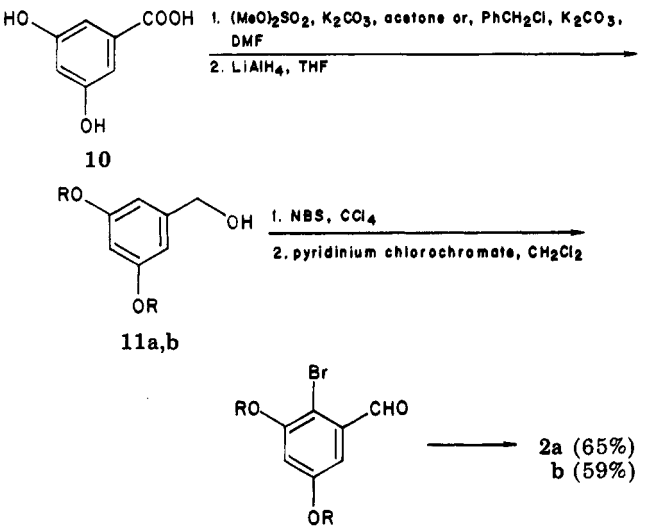
Successful development of the present method was based on the following observations. First, the aldehyde function of a bromobenzaldehyde can be protected in situ by reacting the aldehyde with lithium morpholide to give the corresponding lithium morpholinoalkoxide, stable to organolithium reagents.[15] Recently, we have utilized this in situ method of protection for the synthesis of a variety of alkoxyphthalaldehydic acids and the corresponding phthalides, demonstrating the applicability of this in situ method of protection to complex substrates.[16] The second observation is that phenyllithium reacts with nitrobenzene to give lithium phenoxide at low temperature.[17] Only a few reports[18,19] have appeared where hydroxylation has been carried out by using this method. A significant byproduct in the reaction of an aryllithium with nitrobenzene is the corresponding arene which is formed by the abstraction of an ortho (or para) hydrogen of nitrobenzene by the aryllithium.[18] In spite of these limitations, nitrobenzene appeared to be a better reagent than oxygen[20,21] which is the only alternate reagent available for the direct oxygenation of aryllithiums, both in terms of yields of products and the convenience of use.

The method we developed is illustrated in Scheme I with the synthesis of the hydroxybenzaldehyde **1a** from the corresponding bromobenzaldehyde **4**. The aldehyde function of **4** was protected in situ[15] by reacting **4** at −50 °C with lithium morpholide (**5**) to give **6**. The lithiated morpholinoalkoxide **7** was generated by reacting **6** with *n*-BuLi at −75 °C. Reaction of **7** with nitrobenzene[17] for 4 h at −75 °C followed by an acidic workup furnished the desired hydroxybenzaldehyde **1a** in 55% yield as the only phenolic product. The only nonphenolic byproduct derived from **4** was **9**, isolated in 20% yield based on **4** used. Similar nonphenolic byproducts, derived from the starting bromobenzaldehydes, were formed in all of the examples studied.

Scheme I



Scheme II[a]



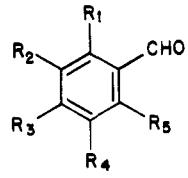
[a] a, R = Me; b, R = CH_2Ph.

For the synthesis of **2a** and **2b** we required the bromobenzaldehydes **12a** and **12b**, respectively (Scheme II). These were synthesized[16] in four steps in excellent overall yields from the readily available dihydroxybenzoic acid **10**. Hydroxylation of **12a** and **12b** was carried out as described in Scheme I for **4** to give the hydroxybenzaldehydes **2a** and **2b** in 65% and 59% yields, respectively. In each case only one phenolic product was detected. In the NMR, both **2a**

(12) Battersby, A. R.; Dobson, T. A.; Foulkes, D. M.; Herbert, R. B. *J. Chem. Soc., Perkin Trans. I* **1972**, 1730–1736.
(13) Borchardt, R. T.; Sinhababu, A. K., manuscript in preparation. For a review on serotonin neurotoxins see: "Serotonin Neurotoxins"; Jacoby, J. H.; Lytle, L. D., Eds. *Ann. N. Y. Acad. Sci.* **1978**, *305*, 1–702.
(14) Royer, R.; Renê, L.; Cavier, R.; Lemoine, J. *Eur. J. Med. Chem.—Chim. Ther.* **1977**, *12*, 455–458.
(15) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213–4216.
(16) Sinhababu, A. K.; Borchardt, R. T. submitted for publication in *J. Org. Chem.*
(17) (a) Buck, P.; Köbrich, G. *Tetrahedron Lett.* **1967**, 1563–1565. (b) Köbrich, G.; Buck, P. *Chem. Ber.* **1970**, *103*, 1412–1419.
(18) Wiriyachitra, P.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 2274–2277.
(19) (a) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91* 3527–3533. (b) Sheehan, M.; Cram, D. J. *Ibid.* **1969**, *91*, 3544–3552.
(20) Gilman, H.; Esmay, D. L. *J. Am. Chem. Soc.* **1954**, *76*, 5787–5788.
(21) The use of alkyl peroxybenzoates permits the direct introduction of alkoxy groups: Hörnfeldt, A. B.; Gronowitz, S. *Ark. Kemi* **1963**, *21*, 239–257; *Chem. Abstr.* **1963**, *59*, 13917*b*. However, yields are often low.[18]

and **2b** displayed characteristic meta coupling with $J_{4,6}$ = 2.9 Hz, and their carbonyl absorptions in the IR occurred at 1660 and 1650 cm^{-1}, respectively, characteristic of *o*-hydroxybenzaldehydes. Formation of only **2a** and **2b** from **12a** and **12b**, respectively, indicates that even though both of these bromobenzaldehydes contain an excellent alternate metalation site (position 4 of **12a,b**), metalation did not take place to any detectable extent at this site.

To determine the generality of the present hydroxylation procedure, we extended this study to the synthesis of the hydroxybenzaldehydes **14**, **16**, and **18**, all of which are



	R_1	R_2	R_3	R_4	R_5
13	Br	OMe	OMe	H	H
14	OH	OMe	OMe	H	H
15	H	OCH_2O		Br	H
16	H	OCH_2O		OH	H
17	H	OMe	OMe	H	Br
18	H	OMe	OMe	H	OH

components of numerous natural products[22-25] and are valuable intermediates for the synthesis of many pharmacologically interesting agents.[26-29]

The hydroxybenzaldehyde **14** was produced[31] in 62% yield from the readily available[16] bromobenzaldehyde **13**. All the three previous methods of synthesis of **14** involved selective demethylation of 2,3,4-trimethoxybenzaldehyde with BCl_3,[30] $AlCl_3$,[23a] or sodium *p*-thiocresolate[32] in modest yields. Conversion of **15** to **16** proceeded in 56% yield. The bromobenzaldehyde **15** was prepared from the corresponding catechol by using a modified procedure (see Experimental Section). The only reported[6] synthesis of **16**, in 39% yield, also started with **15** and used a four-step hydroxylation procedure. Conversion of the bromobenzaldehyde **17**, which is commercially available, to the hydroxybenzaldehyde **18** proceeded in 58% yield. Previously, **18** had been synthesized by selective demethylation of the corresponding trimethoxybenzaldehyde[30] in poor yields and also by the formylation[33] of 3,4-dimethoxy-1-hydroxybenzene which is not readily available.

Smooth hydroxylation of **12a,b** and **13**, all with both the ortho positions to Br substituted, suggests that steric hindrance due to these ortho substituents did not play any significant role since the yields of the corresponding hydroxylated products were comparable to those cases (**4**, **15**, and **17**) where such steric hindrance was absent. Modest yields in this reaction, as mentioned earlier, are due to the limitations of nitrobenzene as a direct oxygenation reagent. Consequently, a significant innovation in this area of aromatic hydroxylation via aryllithiums will be the availability of a nitro compound or other oxygen-donating agent superior to nitrobenzene. Unfortunately, it has been reported[13] that none among a number of seemingly suitable nitro compounds, including 2,4,6-tri-*tert*-butylnitrobenzene was superior to nitrobenzene.

In summary, a mild one-step method for the conversion of bromobenzaldehydes to the corresponding hydroxybenzaldehydes has been developed which appears to be of general applicability.[34]

Experimental Section

General Methods. Infrared spectra were recorded on a Beckman IR-33 spectrophotometer and are reported in reciprocal centimeters. ^1H NMR spectra were recorded 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, anhydrous) was dried over 3-Å molecular sieves and stored under N_2. Morpholine (Fischer) was stored over NaOH pellets under nitrogen in a septum-capped bottle. Nitrobenzene was freshly distilled under reduced pressure from P_2O_5 after being stored over P_2O_5 for 1 day.

General Procedure for Hydroxylation. Morpholine (1.05 g, 12 mmol) and THF (20 mL) were placed in a dry, three-necked, round-bottomed flask equipped with a stirring bar, septum cap, dropping funnel, thermometer, and N_2 inlet. The flask was cooled in a dry ice–acetone bath to −50 °C, and a solution of *n*-BuLi in hexane (1.6 M, 7.5 mL, 12 mmol) was added all at once. After 5 min a solution of the bromobenzaldehyde (10 mmol) in 15 mL of THF was injected over a period of 2 min, and the mixture was allowed to cool to −75 °C over 15 min. *n*-BuLi in hexane (1.6 M, 10 mL, 16 mmol) was then added dropwise, keeping the temperature at ~−75 °C. After 35 min at −75 °C, a solution of $PhNO_2$ (3.45 g, 28 mmol) in 5 mL of THF was added from the dropping funnel, keeping the temperature at −75 °C. The dark mixture was stirred at −75 °C for 4 h and then allowed to warm to room temperature. The mixture was acidified to pH ~1 with 6 N HCl and stirred for 15 min. After dilution with brine, the organic layer was collected, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers (except for the synthesis of **2b**) were extracted with 2 N NaOH (3 × 10 mL). [The dark organic layer after extraction with NaOH contained $PhNO_2$-derived byproducts and the nonphenolic byproduct derived from the bromobenzaldehyde used, e.g., **9** from **4**. Compound **9** and the corresponding nonphenolic byproducts derived from the bromobenzaldehydes **12**, **13**, **15**, and **17**, respectively, were identified by comparison with authentic samples by TLC (silica gel GHLF, Analtech) in CH_2Cl_2.] The combined NaOH extracts were washed with Et_2O (2 × 10 mL) and then acidified to pH ~1 with concentrated HCl. The resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and then passed directly through a short column of silica gel (5 g) in CH_2Cl_2 to remove colored impurities. Further elution with CH_2Cl_2 and evaporation

(22) For **14** see ref 23, for **16** see ref 24, and for **18** see ref 25.

(23) (a) Lupi, A.; Marta, M.; Lintas, G.; Bettolo, G. B. M. *Gazz. Chim. Ital.* **1980**, *110*, 625–628. (b) Tomimatsu, T.; Yamada, S.; Yuasa, R. *Yakugaku Zasshi* **1977**, *97*, 217–222; *Chem. Abstr.* **1977**, *87*, 161436.

(24) Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds. Vol. 1. Acetogenins, Shikimates and Carbohydrates"; Academic Press: New York, 1975.

(25) Bhanu, S.; Seshadri, T. R.; Mukerjee, S. K. *Indian J. Chem.* **1974**, *12*, 20–22.

(26) For **14** see ref 27, for **16** see ref 28, and for **18** see ref 29.

(27) Fatome, M.; Andrieu, L.; Laval, J.-D.; Clavel, J.-M.; Blanco, L.; Guillaumel, J.; Rene, L.; Royer, R. *Eur. J. Med. Chem.—Chim. Ther.* **1977**, *12*, 383–384.

(28) (a) Shulgin, A. T.; Sargent, T.; Narango, C. *Nature (London)* **1969**, *221*, 537–541. (b) Nichols, D. *J. Pharm. Sci.* **1981**, *70*, 839–849.

(29) Kapadia, G. J.; Chowdhury, B. K.; Rao, G. S.; Pradhan, S. N. *J. Pharm. Sci.* **1974**, *63*, 1339–1341.

(30) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. Q.; Somvichien, N. *Tetrahedron Lett.* **1966**, 4153–4159.

(31) Attempts to produce the ring-lithiated intermediate involved in this transformation (cf. **7**) selectively from **9** (as its in situ protected morpholino alkoxide) by lithium–hydrogen exchange using BuLi in Et_2O or THF (up to 25 °C, 4 h) were not successful. A mixture was formed as evidenced by the TLC (silica gel, CH_2Cl_2) of the product mixture obtained following methylation with dimethyl sulfate. Part of the problem may have been the competitive metalation arising from the methoxy groups as well as the morpholino alkoxide group.[34]

(32) Hansson, C.; Wickberg, B. *Synthesis* **1976**, 191–192.

(33) Head, F. S. H.; Robertson, A. *J. Chem. Soc.* **1930**, 2434–2444.

(34) After the submission of the present work for publication, a report appeared (Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, 3979–3982) describing the directed ortho lithiation of α-(*N*-methylpiperazino)benzyl alkoxides (derived in situ from benzaldehydes) by using BuLi in refluxing benzene. This development, together with the results of our investigation, may lead to a new method for the selective ortho hydroxylation of suitable benzaldehydes.

of solvent gave essentially pure, solid product. Solvents for recrystallization and physical properties of the individual hydroxybenzaldehydes are described below.

3,4-Dimethoxy-5-hydroxybenzaldehyde (1a) from 4[6] was recrystallized from toluene–hexane: 1 g (55%); mp 64–65 °C (lit. mp 64–65 °C,[6] 60–61 °C,[11] 70–72 °C[12]); IR (Neat) 3480, 1690, 1590 cm^{-1}; NMR ($CDCl_3$) δ 3.83 (s, 3, OMe), 3.89 (s, 3, OMe), 6.98 (d, $J_{2,6}$ = 1.5 Hz, 1, H-6), 7.06 (d, $J_{2,6}$ = 1.5 Hz, 1, H-2), 7.24 (br s, 1, OH), 9.73 (s, 1, CHO).

3,5-Dimethoxy-2-hydroxybenzaldehyde (2a) from 12a[16] was recrystallized from CH_3OH to give pale yellow, silky needles: 1.18 g (65%); mp 129.5–130.5 °C (lit.[14] mp 129 °C); IR (Nujol) 3210, 1660, 1605 cm^{-1}; NMR ($CDCl_3$) δ 3.79 (s, 3, OMe), 3.88 (s, 3, OMe), 6.56 (d, $J_{4,6}$ = 2.9 Hz, 1, H-4), 6.75 (d, $J_{4,6}$ = 2.9 Hz, 1, H-6), 9.90 (s, 1, CHO), 10.62 (s, 1, OH).

3,5-Bis(benzyloxy)-2-hydroxybenzaldehyde (2b) from 12b.[16] To the combined organic layers (see the general procedure above) was added 40 mL of 2 N NaOH, and the resulting mixture was stirred vigorously for 30 min. The precipitated solid (the sodium salt of the phenol **2b**) was collected by filtration and was washed with Et_2O. The solid was then placed in a mixture of 50 mL of CH_2Cl_2 and 40 mL of 4 N HCl, and the resulting mixture was stirred until all the solid dissolved. The organic layer was collected, washed with brine, dried (Na_2SO_4), and then passed directly through a column of silica gel (10 g) in CH_2Cl_2. Further elution with CH_2Cl_2 and evaporation of eluents gave a solid residue which was recrystallized from CH_3OH, affording **2b** as yellow needles: 1.98 g (59%); mp 97–99 °C; IR (Nujol) 1650, 1595 cm^{-1}; NMR ($CDCl_3$) δ 4.92 (s, 2, OCH_2), 5.05 (s, 2, OCH_2), 6.62 (d, $J_{4,6}$ = 2.9 Hz, 1, H-4), 6.81 (d, $J_{4,6}$ = 2.9 Hz, 1, H-6), 7.81 (s, 10, Ph), 9.76 (s, 1, CHO), 10.52 (s, 1, OH). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.60; H, 5.58.

3,4-Dimethoxy-2-hydroxybenzaldehyde (14) from 13[16] was recrystallized from benzene–hexane to give white plates: 1.13 g (62%); mp 70–72 °C (lit.[32] mp 70–72 °C); IR (Nujol) 1640, 1590 cm^{-1}; NMR ($CDCl_3$) δ 3.86 (s, 3, OMe), 3.93 (s, 3, OMe), 6.58 (d, $J_{5,6}$ = 9 Hz, 1, H-5), 7.27 (d, $J_{5,6}$ = 9 Hz, 1, H-6), 9.71 (s, 1, CHO), 11.17 (s, 1, OH).

3-Hydroxy-4,5-(methylenedioxy)benzaldehyde (16) from 15 was recrystallized from toluene to give amorphous solid: 930 mg (56%); mp 133–134 °C (lit.[6] mp 134–134.5 °C); IR (Nujol) 3260, 1650, 1605 cm^{-1}; NMR (acetone-d_6) δ 6.10 (s, 2, OCH_2O), 6.92 (d, $J_{2,6}$ = 1.5 Hz, 1, H-2), 7.12 (d, $J_{2,6}$ = 1.5 Hz, 1, H-6), 8.80 (br s, 1, OH), 9.74 (s, 1, CHO).

4,5-Dimethoxy-2-hydroxybenzaldehyde (18) from 17 (Aldrich) was recrystallized from benzene–hexane to give off-white solid: 1.06 g (58%); mp 104–106 °C (lit.[32] mp 105 °C); IR (Nujol) 1630, 1592 cm^{-1}; NMR ($CDCl_3$) δ 3.84 (s, 3, OMe), 3.90 (s, 3, OMe), 6.44 (s, 1, H-3), 6.89 (s, 1, H-6), 9.68 (s, 1, CHO), 11.38 (s, 1, OH).

3-Bromo-4,5-(methylenedioxy)benzaldehyde (15). To a stirred solution 3-bromo-4,5-dihydroxybenzaldehyde[35] (5.43 g, 25 mmol) in 75 mL of dry DMF under an N_2 atmosphere was added anhydrous KF (PCR Inc., anhydrous material freshly dried at 0.01 mm over P_2O_5 for 24 h, 7.25 g, 125 mmol). After 15 min, CH_2Br_2 (4.79 g, 27.5 mol) was added, and the mixture was heated at 105 °C with stirring for 2 h. The mixture was then evaporated in vacuo to dryness, and the residue was extracted 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 an off-white solid which was recrystallized from benzene–hexane to afford **15**: 4.80 g (85%); mp 125–127 °C (lit.[36] mp 124–126 °C); IR (Nujol) 1685, 1595 cm^{-1}; NMR ($CDCl_3$) δ 6.09 (s, 2, OCH_2O), 7.21 (d, $J_{2,6}$ = 1.6 Hz, 1, H-2), 7.48 (d, $J_{2,6}$ = 1.6 Hz, 1, H-6), 9.72 (s, 1, CHO).

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Registry No. **1a**, 29865-90-5; **2a**, 65162-29-0; **2b**, 85565-92-0; **4**, 6948-30-7; **9**, 120-14-9; **12a**, 85565-93-1; **12a** (debromo derivative), 7311-34-4; **12b**, 85565-94-2; **12b** (debromo derivative), 14615-72-6; **13**, 55171-60-3; **14**, 19283-70-6; **15**, 19522-96-4; **15** (debromo derivative), 120-57-0; **16**, 81805-98-3; **17**, 5392-10-9; **18**, 14382-91-3; 3-bromo-4,5-dihyroxybenzaldehyde, 16414-34-9; dibromomethane, 74-95-3; morpholine, 110-91-8; butyllithium, 109-72-8.

(35) Lange, R. G. *J. Org. Chem.* **1962**, *27*, 2037–2039.
(36) Ishii, H.; Ueda, E.; Nakajima, K.; Ishida, T.; Ishikawa, T.; Harada, K.-I.; Ninomiya, I.; Naito, T.; Kiguchi, T. *Chem. Pharm. Bull.* **1978**, *26*, 864–873.

Electrooxidative Cleavage of Carbon–Carbon Bonds. 2. Double Cleavage of α,β-Epoxyalkanones and Enantiospecific Syntheses of Chiral Methyl *trans*- and *cis*-Chrysanthemates from (+)- and (−)-Carvones

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The stereospecific synthesis of chiral methyl *trans*- and *cis*-chrysanthemates (**1** and **26**) from (+)- and (−)-carvones (**7a,b**) is described. Methyl (3*R*)- and (3*S*)-3-(1-chloro-1-methylethyl)-5-oxohexanoates (**3**) and methyl (3*S*)- and (3*R*)-3-(1-chloro-1-methylethyl)-5,5-dimethoxypentanoates (**4**) are key intermediates in the preparation of **1** and **26** via δ-lactone **2**. Electrochemical cleavage of 5-(1-chloro-1-methylethyl)-2,3-epoxy-2,3-dimethylcyclohexan-1-one (**5**) at the C-1 and C-2 positions in the MeOH–AcOEt (7:1)–0.047 M $LiClO_4$–(Pt) system gave **3** in 86–90% yields. Each enantiomer of **5** was prepared from **7** through four steps in approximately 63% overall yields. Enantiomers **4** were obtained by the electrolysis of 3-hydroxy-2-methoxy- or 2-hydroxy-3-methoxy-5-(1-chloro-1-methylethyl)-2-methylcyclohexan-1-ones (**14** or **15**) in 87% yield. The precursors **14** and **15** were smoothly provided by acid-catalyzed methanolysis of epoxides **6** prepared from **7**. Methylation of **3** with methylmagnesium iodide and geminal dimethylation of **4** with methyllithium followed by oxidation with chromic acid gave the same product **2**. Cyclization of **2** with lithium diisopropylamide gave dihydrochrysanthemolactone (**23**; 80% yield from **3** and 50% yield from **4**, respectively). The conversion of **23** to the desired **1** was achieved by treatment with sodium hydroxide at 230–235 °C in 58–59% yields. The cis isomers **26** were also prepared from **23** by hydrolysis followed by dehydration and subsequent isomerization of the double bond in 80% yield.

The use of chiral synthons derived from biomass for the synthesis of chiral, bioactive compounds has been of current interest.[1] The preparation of chiral *trans*- and *cis*-chrysanthemic acids (**1** and **26**; R = H) is of key importance

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