Aromatic Lithiation Directed by the Carboxylic Acid Groups. Synthesis of 9-Substituted Dibenzodioxin-1-carboxylic Acids and 6-Substituted Phenoxathiin-4-carboxylic Acids

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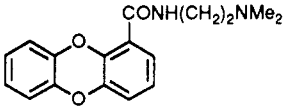
An efficient procedure has been developed for the regiospecific synthesis of 9-substituted dibenzo[1,4]dioxin-1-carboxylic acid derivatives. Lithiation of dibenzo[1,4]dioxin-1-carboxylic acid forms the lithium carboxylate, which directs subsequent metalation exclusively to the 9-position. Conditions for the controlled mono- and dilithiation of dibenzo[1,4]dioxin itself, leading to the direct synthesis of the corresponding mono- and isomeric dimethyl esters, are also described.

The directed metalation of aromatic and heteroaromatic ring systems is now a useful technique for the regiospecific introduction of new functionality into such systems.[1] The large range of substituents capable of functioning as directors of metalation includes groups which undergo metalation themselves prior to the aromatic system, leading to dimetalated species, for example, benzyl alcohols, aryl amides, thioamides, sulfonamides, and anilides.[2] More recently the lithium salts of "acidic" substituents such as phenols,[3] thiophenols,[4] and arenesulfonic acids[5] have been identified as effective ortho-metalation directors.

We recently reported that the dibenzo[1,4]dioxin-1-carboxamide (1) has significant in vitro and in vivo antitumor activity,[6] and as part of a program to prepare ring-substituted derivatives of 1 we required a general route to substituted dibenzodioxin-1-carboxylic acids. We report here that, in the case of the dibenzodioxin and certain related ring systems, the carboxylate salt can act as an activating and directing group in metalation reactions.



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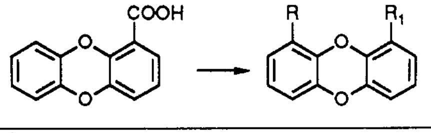
Carboxylic acid functionality is usually considered to be incompatible with lithiation conditions because of its ready reaction to form ketones.[7]

$$\mathrm{ArCOOH} \xrightarrow{\mathrm{RLi}} \mathrm{ArCOOLi} \xrightarrow{\mathrm{RLi}} \mathrm{ArCOR}$$

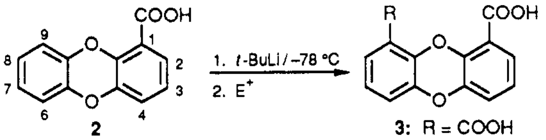
However, dibenzodioxin-1-carboxylic acid (2) reacts with 2 molar equiv of *tert*-butyllithium at –78 °C to give a single diacid (3) following treatment with CO_2. The site of metalation was determined to be at the 9-position from an X-ray crystallographic analysis of the corresponding dimethyl ester 14, mp 149–152 °C. Good yields of other 9-substituted products were also obtained on quenching with other electrophiles (Table I), indicating totally regioselective deprotonation at the C-9 position. Dibenzodioxin itself is not metalated at all at –78 °C but can be deprotonated smoothly at –30 °C, leading to a range of 1-substituted dibenzodioxins upon quenching with electrophiles such as CO_2, MeI, or DMF.[8] Similarly, 1-methyldibenzodioxin (7) could not be metalated at –78 °C, although reaction with *tert*-butyllithium at –30 °C, followed by quenching with CO_2, afforded a mixture of the 1,9- and 1,6-disubstituted products 4 and 9 in ca. 1:1 ratio (^{1}H NMR analysis). Thus, in the case of dibenzodioxin-1-carboxylic acid (2), where metalation occurs at –78 °C and gives solely 9-substituted products, there must be

Table I. Metalation of Dibenzodioxin-1-carboxylic Acid[a]

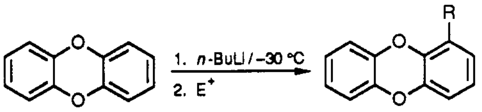


electrophile[b]	product	yield, %
CO_2	R = COOMe; R^1 = COOMe[d] (14)	75
MeI	R = Me; R^1 = COOH (4)	73
Me_3SiCl	R = $SiMe_3$; R^1 = COOH (5)	60
NCS[c]	R = Cl; R^1 = COOH (6)	74
CCl_3CCl_3	R = Cl; R^1 = COOH (6)	68

[a] See Experimental Section for a representative procedure. [b] With the exception of the CO_2 quench, reactions used 2.0 molar equiv of the electrophile. Liquids were added neat; solid electrophiles were added as concentrated solutions in THF. [c] *N*-Chlorosuccinimide. [d] In the case of the CO_2 quench, owing to solubility problems associated with the diacid product 3, the crude reaction mixture was esterified directly prior to workup (see Experimental Section).



3: R = COOH
4: R = Me
5: R = $SiMe_3$
6: R = Cl



2: R = COOH
7: R = Me
8: R = CHO

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(1) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Wardell, J. L. In *the Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Ed.; Wiley: New York, 1987; Vol. 4, p 1. (c) Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67.

(2) For a comprehensive list of references, see ref 4a.

(3) (a) Saa, J. M.; Llobera, A.; Garcia-Raso, A.; Costa, A.; Deya, P. M. *J. Org. Chem.* **1988**, *53*, 4263. (b) Coll, G.; Morey, J.; Costa, A.; Saa, J. M. *J. Org. Chem.* **1988**, *53*, 5345.

(4) (a) Figuly, G. D.; Loop, C.; Martin, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 654. (b) Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.* **1989**, *111*, 658. (c) Smith, K.; Lindsay, C. M.; Pritchard, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 665.

(5) Figuly, G. D.; Martin J. C. *J. Org. Chem.* **1980**, *45*, 3728.

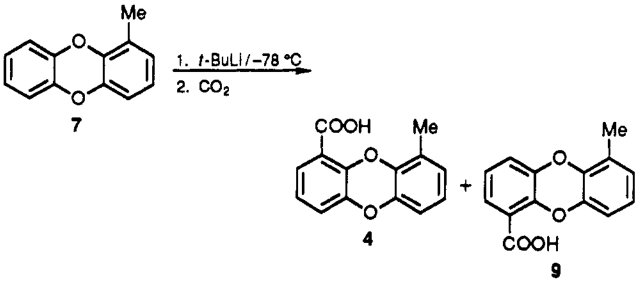
(6) Palmer, B. D.; Rewcastle, G. W.; Atwell, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1988**, *31*, 707.

(7) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1.

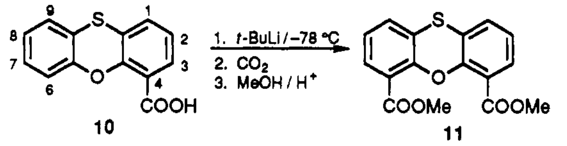
(8) Gilman first reported the metalation of dibenzodioxin at room temperature, to give the 1-carboxylic acid in 10% yield. Gilman, H.; Stuckwisch, C. G. *J. Am. Chem. Soc.* **1943**, *65*, 1461.

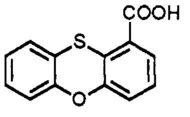
0022-3263/90/1955-0438$02.50/0

activation and direction of the ring metalation by the initially formed ArCOOLi group.[9]



Similar carboxylate-directed metalation has also been observed in the phenoxathiin ring system. When phenoxathiin-4-carboxylic acid (**10**) was reacted with *tert*-butyllithium at –78 °C, followed by quenching with CO_2 and esterification, the symmetrical 4,6-diester **11** was obtained as the sole product in 69% yield. However a similar reaction using the isomeric 1-acid **12** gave only starting material, presumably due to the reduced ability of sulphur compared with oxygen to activate an ortho-metalation site.[6,10] It is interesting to note that in both the dibenzodioxin and phenoxathiin cases, the carboxylic acid substituent is unreactive to *n*- or *tert*-butyllithium at temperatures of up to –20 °C, whether or not metalation of the ring occurs. In contrast, when *m*-anisic acid was reacted with *tert*-butyllithium at –78 °C no evidence of lithiation was observed and only the *tert*-butyl ketone **13** was isolated, together with starting material.





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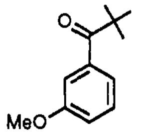

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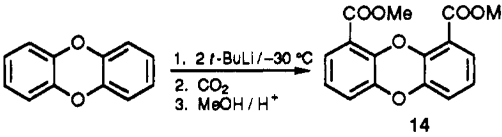
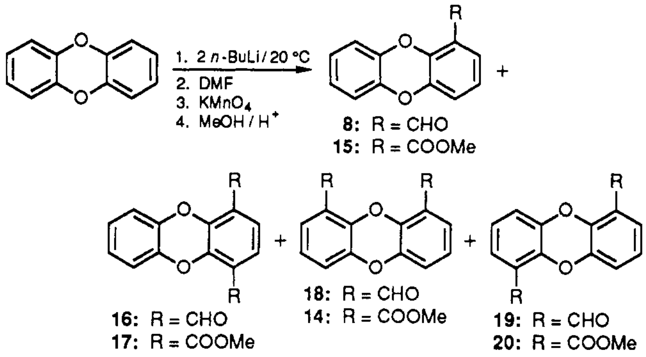
Although the carboxylate group is clearly functioning as a metalation director in the cases of the acids **2** and **10**, it is clear from the isomeric phenoxathiin acid examples that additional activation of the 9-position by the *o*-oxygen functionality is also required; the unusually unreactive carboxylate anion and the ether oxygen are thus working in concert to bring about the regiospecific metalation.

When dibenzodioxin was reacted with 2 molar equiv of *tert*-butyllithium at –30 °C and quenched with CO_2 followed by esterification, a good yield of the 1,9-diester **14** was obtained, suggesting that a 1,9-dianion might have been generated under these conditions. However, when the electrophile was changed to methyl iodide, only 1-methyldibenzodioxin (**7**) was isolated, indicating that at this temperature only monometalation occurs to any appreciable extent. It seems likely that in the special case of quenching with CO_2 the initially formed 1-carboxylate salt is able to direct a subsequent deprotonation of the 9-position during the quench. Katritzky has recently described[11] procedures for the regiospecific metalation of nitrogen-containing heterocycles in which an in situ formed *N*-carboxylate is used to activate the subsequent C-lithiation step, although in these cases the lithiating reagents were usually added sequentially.



However, lithiation of dibenzodioxin at room temperature did provide evidence of dimetalation, although yields were not synthetically useful. Treatment of dibenzodioxin in ether with 2 molar equiv of *n*-butyllithium at 20 °C for 48 h, followed by quenching with DMF, led to a complex mixture of aldehydes, together with a large amount of polymeric material. Extensive chromatography gave pure aldehydes, which were oxidized with $KMnO_4$ and esterified to provide small quantities of dibenzodioxin-1-carboxylic ester (**15**) as well as three diesters (**17**, **14**, and **20**).[12]



The structure of the 1,4-diester **17**, mp 119–120 °C, was evident from an examination of its ^1H NMR spectrum, where a 2-proton singlet at δ 7.39 obviously resulted from the equivalent Ar-H_2 and Ar-H_3 protons. The other two compounds had broadly similar ^1H NMR spectra, indicating that the second ester function was in the other ring in each case. One was the known 1,9-diester of mp 149–152 °C obtained above and was identified by melting point and identity of NMR spectra. The remaining compound of mp 204 °C was thus identified as the 1,6-diester **20**. Gilman[8] had metalated dibenzodioxin in refluxing ether using a large excess of methyllithium and carbonated the product. Fractional crystallization afforded low yields of two unidentified diesters, melting at 142–143 °C and 202–204 °C, and now clearly identified by this work as the 1,9- and 1,6-diesters respectively.[13]

Conclusions

The present work provides a rare example of the carboxylate group functioning as a metalation director in lithiation reactions. Since electrophiles are now available for introduction of a large range of functional groups, the present procedure provides a general route to 9-substituted

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[9] Another example of the successful metalation of a heteroaromatic carboxylic acid has been reported: Caton, M. P. L.; Jones, D. H.; Slack, R.; Woolridge, K. R. H. *J. Chem. Soc.* **1964**, 446.

[10] Gilman, H.; van Ess, M. W.; Willis, H. B.; Stuckwisch, C. G. *J. Am. Chem. Soc.* **1940**, *62*, 2606. Metalation of phenoxathiin occurs at –30 °C, leading to products in which metalation occurs adjacent to the oxygen atoms (see ref 6).

[11] Katritzky, A. R.; Rewcastle, G. W.; Lam, J. N.; Sengupta, S. In *Progress in Heterocyclic Chemistry*; Pergamon Press: New York, 1989; Vol. 1, Chapter 1.

[12] When methyl iodide was substituted for DMF as the electrophile in this reaction, an inseparable mixture of 1-methyldibenzodioxin together with isomeric dimethyldibenzodioxins was produced (^1H NMR and MS analyses), again indicating the presence of dilithiated intermediates.

[13] Ueda reported the preparation of the 1,6-diester **20**, mp 214 °C, but it is not clear whether his procedure could have unambiguously distinguished this from the 1,9-isomer **14**: Ueda, S. *Yakugaku Zasshi* **1962**, *82*, 714; **1963**, *83*, 802; *Chem. Abstr.* **1963**, *58*, 3419*g*; **1963**, *59*, 15279*g*.

dibenzodioxin-1-carboxylic acids and 6-substituted phenoxathiin-4-carboxylic acids.

Experimental Section

Melting points were determined on an Electrothermal apparatus and are uncorrected. NMR spectra were measured on a Bruker AM-400 spectrometer in $CDCl_3$ and are referenced to Me_4Si. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl immediately prior to use. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was distilled from CaH_2 onto activated 4A molecular sieves. All metalation reactions were performed under an atmosphere of dry N_2, using oven-dried glassware. CO_2 gas was dried by passage through a column of soda lime. Elemental analyses were carried out in the Microchemical Laboratory, University of Otago, New Zealand.

Lithiation of Dibenzodioxin-1-carboxylic Acid (2). A solution of the acid **2** (1.00 g, 4.38 mmol) and TMEDA (0.73 mL, 4.82 mmol) in THF (50 mL) was cooled to −78 °C and treated with *tert*-butyllithium (5.28 mL of 1.70 N solution in pentane, 8.98 mmol), and the solution was stirred at this temperature for 1 h. CO_2 gas was bubbled through as the mixture warmed to room temperature, and the solution was then concentrated to dryness under reduced pressure. The residue was dissolved in MeOH (30 mL) containing concentrated H_2SO_4 (3 mL) and heated under reflux for 3 h before being poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. Workup gave a solid, which was chromatographed on silica. Elution with EtOAc/petroleum ether (1:50) gave dimethyl dibenzo[1,4]dioxin-1,9-dicarboxylate (**14**) (1.12 g, 75%), which crystallized from Me_2CO as rods: mp 149–152 °C; ^1H NMR ($CDCl_3$) δ 7.44 (dd, J = 7.52 and 2.12 Hz, 2 H, $H_{2,8}$), 6.99 (dd, J = 8.03 and 2.12 Hz, 2 H, $H_{4,6}$), 6.95 (dd, J = 8.03 and 7.52 Hz, 2 H, $H_{3,7}$), 3.96 (s, 6 H, COOMe). Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: C, 63.79; H, 4.04.

The remaining products in Table I were isolated as the free acids, following chromatography on silica, using EtOAc as eluant.

9-Methyldibenzo[1,4]dioxin-1-carboxylic acid (4): mp 220–222 °C ($CHCl_3$/petroleum ether); ^1H NMR ($CDCl_3$) δ 7.64 (dd, 1 H, J = 7.86 and 1.24 Hz, ArH_2), 7.07 (dd, 1 H, J = 7.86 and 1.24 Hz, ArH_4), 6.99 (dd, 1 H, J = 7.86 and 7.86 Hz, ArH_3), 6.86 (dd, 1 H, J = 7.57 and 7.61 Hz, ArH_7), 6.81 (dd, J = 7.57 and 1.20 Hz, ArH_6), 6.73 (dd, 1 H, J = 7.61 and 1.23 Hz, ArH_8), 2.32 (s, 3 H, Me). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.71; H, 3.95.

9-(Trimethylsilyl)dibenzo[1,4]dioxin-1-carboxylic acid (5): mp 200 °C ($CHCl_3$/petroleum ether); ^1H NMR ($CDCl_3$) δ 7.54 (dd, 1 H, J = 7.88 and 1.74 Hz, ArH_2), 7.03 (dd, J = 7.97 and 1.74 Hz, ArH_4), 7.00 (dd, 1 H, J = 7.27 and 1.70 Hz, ArH_8), 6.94 (dd, 1 H, J = 7.88 and 7.97 Hz, ArH_3), 6.92 (dd, 1 H, J = 7.81 and 7.27 Hz, ArH_7), 6.85 (dd, 1 H, J = 7.81 and 1.67 Hz, ArH_6), 0.36 (s, 9 H, $SiMe_3$). Anal. Calcd for $C_{16}H_{16}SiO_4$: C, 63.97; H, 5.37. Found: C, 63.95; H, 5.72.

9-Chlorodibenzo[1,4]dioxin-1-carboxylic acid (6): mp 221–224 °C (EtOAc/petroleum ether); ^1H NMR ($CDCl_3$) δ 7.74 (dd, 1 H, J = 7.84 and 1.91 Hz, ArH_2), 7.12 (dd, 1 H, J = 8.09 and 1.91 Hz, ArH_4), 7.07 (dd, 1 H, J = 8.09 and 7.84 Hz, ArH_3), 7.06 (dd, 1 H, J = 8.25 and 1.54 Hz, ArH_8), 6.95 (dd, 1 H, J = 8.25 and 8.09 Hz, ArH_7), 6.84 (dd, 1 H, J = 8.09 and 1.48 Hz, ArH_6). Anal. Calcd for $C_{13}H_7ClO_4$: C, 59.44; H, 2.69; Cl, 13.50. Found: C, 59.01; H, 2.34; Cl, 13.23.

In an identical manner phenoxathiin-4-carboxylic acid (**10**)[14] (0.41 g) was metalated, quenched with CO_2, and esterified during workup. Chromatography on silica, eluting with EtOAc–petroleum ether (1:5), gave the 4,6-dimethyl ester **11** (0.42 g, 69%), which crystallized from $CHCl_3$/petroleum ether as yellow cubes: mp 68–70 °C; ^1H NMR ($CDCl_3$) δ 7.50 (dd, J = 7.73 and 1.62 Hz, 2 H, $ArH_{3,7}$), 7.24 (dd, J = 7.73 and 1.62 Hz, 2 H, $ArH_{1,9}$), 7.07 (t, 2 H, J = 7.73 Hz, $ArH_{2,8}$), 3.96 (s, 6 H, COOMe). Anal. Calcd for $C_{16}H_{12}O_5S$: C, 60.76; H, 3.82; S, 10.12. Found: C, 60.83; H, 3.59; S, 10.28.

Lithiation of Dibenzodioxin. Representative Procedure. A solution of dibenzodioxin (2.00 g, 10.8 mmol) and TMEDA (1.8 mL, 11.9 mmol) in THF (40 mL) was cooled to −30 °C and treated with *n*-BuLi (7.6 mL of 1.50 N solution in hexane, 11.4 mmol). After 1 h, dry CO_2 gas was passed through the yellow suspension, and the mixture was allowed to rise to room temperature and poured into Et_2O. The solution was extracted into 2 N NaOH, acidified, extracted into CH_2Cl_2, and worked up to give crude dibenzodioxin-1-carboxylic acid (**2**) as a white solid. This was dissolved in MeOH (30 mL) containing concentrated H_2SO_4 (3 mL), and the solution was heated under reflux for 4 h and poured into saturated aqueous $NaHCO_3$. Extraction with EtOAc and workup gave a solid, which was chromatographed on silica. Elution with petroleum ether/EtOAc (10:1) gave methyl dibenzo[1,4]dioxin-1-carboxylate (**15**) (2.11 g, 80%), which crystallized from petroleum ether as cubes: mp 88 °C (lit.[8] mp 86 °C); ^1H NMR ($CDCl_3$) δ 7.41 (dd, J = 7.85 and 1.71 Hz, 1 H, ArH_2), 6.97 (dd, J = 8.01 and 1.71 Hz, 1 H, ArH_4), 6.95–6.87 (m, 4 H, $ArH_{3,7,8,9}$), 6.84–6.81 (m, 1 H, ArH_6), 3.91 (s, 3 H, COOMe). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.53; H, 3.98.

Elution with EtOAc/petroleum ether (1:5) gave dimethyl dibenzo[1,4]dioxin-1,9-dicarboxylate (**14**) (0.41 g, 12%), which crystallized from Me_2CO as coarse rods, mp 140–142 °C, identical with an authentic sample.

Hydrolysis of **15** using 3 N KOH in MeOH gave dibenzo[1,4]dioxin-1-carboxylic acid (**2**) (100%), which crystallized from EtOAc/petroleum ether as a cream powder, mp 207 °C (lit.[8] mp 210 °C).

In a similar fashion, quenching the lithiation reaction with MeI afforded 1-methyldibenzo[1,4]dioxin (**7**) (80%): mp 110–112 °C (MeOH); ^1H NMR ($CDCl_3$) δ 6.89–6.70 (m, 6 H, ArH), 6.65 (dd, J = 8.5 and 1.9 Hz, 1 H, ArH_2), 2.23 (s, 3 H, Me). Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.08. Found: C, 79.09; H, 4.92. Quenching with DMF gave dibenzo[1,4]dioxin-1-carboxaldehyde (**8**) (84%): mp 105–107 °C (petroleum ether) (lit.[15] no mp reported); ^1H NMR ($CDCl_3$) δ 10.33 (s, 1 H, CHO), 7.36 (dd, 1 H, J = 7.80 and 1.71 Hz, ArH_2), 6.96 (dd, 1 H, J = 7.93 and 1.71 Hz, ArH_4), 6.93–6.84 (m, 4 H, $ArH_{3,7,8,9}$), 6.80 (m, 1 H, ArH_6). Anal. Calcd for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.69; H, 4.15.

Lithiation of 1-Methyldibenzodioxin (7). *tert*-Butyllithium (1.21 mL of a 1.50 N solution in pentane, 1.81 mmol) was added dropwise at −30 °C to a solution of the dibenzodioxin (**7**) (0.35 g, 1.77 mmol) in THF (5 mL). After 1 h, CO_2 gas was passed through the solution as it was warmed to room temperature. The solution was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the aqueous portion was acidified, extracted with EtOAc, and worked up to give an ca. 1:1 mixture of the isomers **4** and **9** (0.29 g, 57%) as an inseparable white solid. Structural assignments were made by comparison of the ^1H and ^{13}C spectra of the mixture with those of **4** prepared earlier and of **9** synthesized by an unambiguous route in these laboratories.[16]

Reaction of *m*-Anisic Acid with *tert*-Butyllithium and Carbon Dioxide. *tert*-Butyllithium (4.31 mL of a 1.60 N solution in pentane, 6.90 mmol) was added dropwise at −78 °C to a solution of *m*-anisic acid (0.50 g, 3.29 mmol) in THF (25 mL). After 45 min, CO_2 gas was passed through the solution as it was warmed over 1 h to room temperature. The solution was poured into water, acidified, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ and worked up to give (3-methoxyphenyl) *tert*-butyl ketone (**13**) (0.36 g, 57%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.40–6.81 (m, 4 H, ArH), 3.80 (s, 3 H, OMe), 1.31 (s, 9 H, CMe_3); mass spectrum found M^+ 192.1146, calcd for $C_{12}H_{16}O_2$ 192.1150. The $NaHCO_3$ washings were acidified, extracted into EtOAc, and worked up to give a mixture of *m*-anisic acid and 2,2-dimethylpropionic acid (0.31 g) (^1H NMR analysis).

Attempted Formation of a Dibenzodioxin Dianion at −30 °C. A solution of dibenzodioxin (1.00 g, 5.43 mmol) and TMEDA (1.80 mL, 11.9 mmol) in THF (30 mL) was treated at −30 °C with *t*-BuLi (7.42 mL of a 1.50 N solution in pentane, 11.0 mmol). After 3 h, dry CO_2 was passed through the suspension for 10 min, and the solution was concentrated completely to dryness. The residue was dissolved in MeOH (50 mL) containing concentrated H_2SO_4

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[14] See ref 6 for procedures to prepare phenoxathiin-1-carboxylic acid and phenoxathiin-4-carboxylic acid.

[15] Vasiliu, G.; Baciu, I. *Rev. Chim.* (*Bucharest*) **1973**, *24*, 413; *Chem. Abstr.* **1974**, *80*, 82843r.

[16] Lee, H. H.; Denny, W. A. Manuscript submitted to *J. Chem. Soc., Perkin Trans. 1*.

(3 mL) and heated under reflux for 3 h. The mixture was then poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc, and the extract was chromatographed on silica. Elution with EtOAc/petroleum ether (1:10) gave methyl dibenzo[1,4]dioxin-1-carboxylate (**15**) (28 mg), mp and mixed mp 88 °C, and EtOAc/petroleum ether (1:4) gave dimethyl dibenzo[1,4]dioxin-1,9-dicarboxylate (**14**) (0.94 g, 58%), mp and mixed mp 145–146 °C. When MeI (2.2 equiv) was substituted for CO_2, only 1-methyldibenzo[1,4]dioxin (**7**) (76%) was isolated.

Metalation of Dibenzodioxin at Room Temperature. *n*-Butyllithium (80.5 mL of a 1.54 N solution in hexane, 0.12 mol) was added at room temperature to a solution of dibenzodioxin (10.0 g, 0.054 mol) in Et_2O (150 mL), and the mixture was stirred at this temperature for 48 h and then cooled to −70 °C. Dimethylformamide (12.0 mL, 0.15 mol) was added rapidly, and the mixture was stirred for a further 10 min and poured into EtOAc. The mixture was filtered to remove an insoluble, yellow polymeric material (4.55 g), and the filtrate was washed well with water and worked up to give an oil (12.7 g), which was chromatographed on silica. Elution with EtOAc/petroleum ether (1:10) gave dibenzo[1,4]dioxin-1-carboxaldehyde (**8**) (0.31 g) (identical with that obtained earlier). Elution with EtOAc/petroleum ether (3:20) gave dibenzo[1,4]dioxin-1,4-dicarboxaldehyde (**16**) (0.84 g) as a deep yellow waxy solid: ^1H NMR ($CDCl_3$) δ 10.44 (s, 2 H, CHO), 7.44 (s, 2 H, $ArH_{2,3}$), 7.04–6.95 (AA′BB′ system, 4 H, $ArH_{6,7,8,9}$). Further elution with EtOAc/petroleum ether (3:20) gave a yellow solid (1.05 g), containing mostly dibenzo[1,4]dioxin-1,6-dicarboxaldehyde (**19**): ^1H NMR ($CDCl_3$) δ 10.43 (s, 2 H, CHO), 7.50 (dd, 2 H, J = 7.89 and 1.81 Hz, $ArH_{2,6}$), 7.11 (dd, 2 H, J = 7.99 and 1.81 Hz, $ArH_{4,9}$), 7.06 (dd, 2 H, J = 7.99 and 7.89 Hz, $ArH_{3,7}$). Later fractions of the same eluant contained mostly dibenzo[1,4]dioxin-1,9-dicarboxaldehyde (**18**) (0.49 g): ^1H NMR ($CDCl_3$) δ 10.39 (s, 2 H, CHO), 7.42 (dd, 2 H, J = 7.82 and 1.57 Hz, $ArH_{2,8}$), 7.06 (dd, 2 H, J = 7.92 and 1.60 Hz, $ArH_{4,6}$), 6.94 (dd, 2 H, J = 7.92 and 7.82 Hz, $ArH_{3,7}$).

Oxidation of the Aldehydes: Representative Procedure. Dimethyl Dibenzo[1,4]dioxin-1,4-dicarboxylate (17). Finely ground $KMnO_4$ (1.6 g, 10.4 mmol) was added in portions over 1 h to a stirred solution of the 1,4-dialdehyde **16** (0.84 g, 3.45 mmol) in Me_2CO (10 mL), after which time no starting material was evident by TLC analysis. The mixture was concentrated to dryness under reduced pressure, and the residue was triturated with 5 N NaOH and filtered. The filtrate was acidified with concentrated HCl to give the crude diacid as a yellow solid (0.81 g, 85%). This was dried under vacuum over silica gel and then esterified by heating under reflux in MeOH (30 mL) containing concentrated H_2SO_4 (2 mL). Workup gave a solid, which was chromatographed on silica. Elution with EtOAc/petroleum ether (3:20) gave dimethyl dibenzo[1,4]dioxin-1,4-dicarboxylate (**17**) (0.76 g, 85%), which crystallized from $CHCl_3$/petroleum ether as cubes: mp 119–120 °C; ^1H NMR ($CDCl_3$) δ 7.39 (s, 2 H, $ArH_{2,3}$), 6.95 (m, 4 H, $ArH_{6,7,8,9}$), 3.94 (s, 6 H, COOMe). Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: C, 64.02; H, 3.98.

Similar oxidation of the crude 1,6-dialdehyde **19** gave dimethyl dibenzo[1,4]dioxin-1,6-dicarboxylate (**20**), which crystallized as rods from $CHCl_3$/petroleum ether: mp 204 °C; ^1H NMR ($CDCl_3$) δ 7.47 (dd, 2 H, J = 7.98 and 1.67 Hz, $ArH_{2,7}$), 7.11 (dd, 2 H, J = 8.04 and 1.67 Hz, $ArH_{4,9}$), 6.95 (dd, 2 H, J = 8.04 and 7.98 Hz, $ArH_{3,8}$), 3.93 (s, 6 H, COOMe). Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: C, 63.90; H, 4.03.

Similar oxidation of the crude 1,9-dialdehyde **18** gave dimethyl dibenzo[1,4]dioxin-1,9-dicarboxylate (**14**), mp and mixed mp 147–150 °C, and with an ^1H NMR spectrum identical with that of authentic material.

X-ray Crystallography. Dimethyl dibenzo[1,4]dioxin-1,9-dicarboxylate (**14**) crystallized from Me_2CO as colorless orthorhombic crystals, $P2_1P2_1P2_1$; cell constants $a = 5.8969_4$, $b = 13.8492_7$, $c = 16.6800_2$ Å; $z = 4$; $V = 1362.204$ Å^3. Lattice constants and intensity data were measured using Ni-filtered Cu Kα radiation, $\lambda = 1.5418$ Å, on a Nonius CAD-4 diffractometer. The data set consisted of 1332 unique reflections, of which 750 were considered observed ($I > 3\sigma > (I)$). The structure was solved by direct methods using SHELX-S[17] and refined using SHELX-76.[18] The largest shift/esd values during the final refinement were < 0.1. Maximum and minimum peaks in the final difference map were +1.3 and −0.18 eÅ^{-3}, respectively. At convergence R and R_w were 0.0359 and 0.0361, respectively.

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Registry No. **2**, 51689-36-2; **4**, 123701-15-5; **5**, 123701-16-6; **6**, 123701-17-7; **7**, 123701-18-8; **8**, 51689-41-9; **9**, 123701-19-9; **10**, 35051-82-2; **11**, 123701-20-2; **12**, 99420-27-6; **13**, 32578-12-4; **14**, 123701-21-3; **15**, 51689-37-3; **16**, 123701-22-4; **17**, 123701-23-5; **18**, 123701-24-6; **19**, 123701-25-7; **20**, 92965-43-0; *m*-$MeOC_6H_4CO_2H$, 586-38-9; dibenzo[1,4]dioxin, 262-12-4; dibenzo[1,4]dioxin-1,4-dicarboxylic acid, 123701-26-8.

Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, bond angles, and bond distances for **14** and a computer-drawn ORTEP diagram of **14** (8 pages). Ordering information is given on any current masthead page.

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Selective Propargylation of Carbonyl Compounds with Allenylstannane/Alkyllithium Mixed Reagents

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1-Substituted allenyltrialkylstannanes readily undergo transmetalation with an alkyllithium to generate a tetraalkylstannane and an equilibrating mixture of the allenyl- and propargyllithium compounds. The organolithium derivatives react with a variety of aldehydes and ketones at low temperature to give, after aqueous workup, the regioisomeric acetylenic and allenic carbinols in high yields. The degree of the regioselection is highly sensitive to the steric and electronic properties of the carbonyl substrates. Excellent acetylene selectivities are obtainable by combination of the bulky reagents and substrates or by using acylsilanes as carbonyl components. The origin of the regioselectivity is discussed.

Selective methods for nucleophilic allylation and propargylation of carbonyl compounds are still being explored.[1] Allenyl and propargyl metal derivatives are of particular interest since they equilibrate in solution in

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