cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) 0.85-1.9 (m, 11, cyclohexyl), 2.19 (s, 3, CH_3C=O), 2.54 (ABq, J = 9.1 and 17.5 Hz, 1, C*H*HC=O), 2.63 (ABq, J = 3 and 17.5 Hz, 1, CH*H*C=O), 2.88 (br s, 1, OH), 3.77-3.85 (m, 1, C*H*OH).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.26; H, 10.78.

A sample of (4*S*)-4-cyclohexyl-4-hydroxybutan-2-one (*enantio*-**16b**) $[\alpha]_D^{25}$ -53° (*c* 1.1, CCl_4) was prepared by ozonolysis (pentane/ethanol, 1:1) of the previously reported[17] (4*S*)-4-cyclohexyl-4-hydroxy-2-methylbut-1-ene (**17a**, 98% ee). The identity of this material and **16b** was established by GC co-injection. The ^{1}H NMR and IR of this sample were identical with those given for **16b**.

(4*S*)-4-Hydroxydodecan-2-one (16c). By the same procedure used to prepare **16a**, the diastereoisomeric alcohols **12c**/**13c** (0.140 g, 0.51 mmol) were converted to aldol **16c**. Column chromatography[8] (gradient elution, 10-30% ether-hexane) gave the title compound **16c** as a white solid (0.083 g, 81% yield), mp 34-35 °C; $[\alpha]_D^{25}$ +35° (*c* 1.8, CCl_4); IR (film) 3300-3650 (OH), 1700 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) 0.87 (t, J = 7 Hz, 3, CH_3CH_2), 1.20-1.55 (m, 14, 7 × CH_2), 2.18 (s, 3, CH_3C=O), 2.52 (ABq, J = 8.9 and 17.1 Hz, 1, C*H*HC=O), 2.63 (ABq, J = 3 and 17.7 Hz, 1, CH*H*C=O), 2.95 (br s, 1, OH), 3.99-4.08 (m, 1, C*H*OH).

A sample of (4*R*)-4-hydroxydodecan-2-one (*enantio*-**16c**) $[\alpha]_D^{25}$ -37° (*c* 1.3, CCl_4) was prepared by ozonlysis (pentane/ethanol, 1:1) of the previously reported[17] (4*R*)-4-hydroxy-2-methyldodec-1-ene (**17b**, 92% ee). The identity of this material and **16c** was established by GC co-injection. The ^{1}H NMR and IR of this sample were identical with those given above for **16c**.

(2*R*,4*S*)-Oct-7-ene-2,4-diol (*enantio*-5). The stereoselective reduction of aldol **16a** was performed according to the procedure of Narasaka and Pai.[4] Thus aldol **16a** (0.10 g, 0.65 mmol) gave the title compound *enantio*-**5** (0.079 g, 78% yield), $[\alpha]_D^{25}$ -16.9° (*c* 1.1, CCl_4). IR, ^{1}H NMR, and GC co-injection established the identity of *enantio*-**5** with an authentic sample.[16] In order to establish the amount of the 2*S* diastereoisomer present, the diol (*enantio*-**5**) was bis(acetylated) (Ac_2O/pyridine/(4-dimethylamino)pyridine/room temperature/3 h). GC[9] of the diacetate showed the ratio of *enantio*-**5** and its C-2 epimer to be 97:3.

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research. We also express our appreciation of Hoffman-La Roche, Basle, for the gift of a generous sample of (3*S*)-ethyl 3-hydroxybutyrate.

Registry No. **5** (isomer 1), 88390-25-4; **5** (isomer 2), 99340-95-1; **8a**, 105230-22-6; **8b**, 105230-23-7; **8c**, 90457-76-4; **11**, 1833-53-0; **12a**, 105230-24-8; **12b**, 105230-26-0; **12c**, 105230-28-2; **13a**, 105230-25-9; **13b**, 105230-27-1; **13c**, 105230-29-3; **14a**, 105230-32-8; **15a**, 105230-33-9; **16a**, 105230-30-6; **16b**, 93643-66-4; **16c**, 105230-31-7; **17a**, 94340-24-6; **17b**, 94340-23-5; CH_2=$CHCH_2CH_2CHO$, 2100-17-6; $CH_3(CH_2)_7CHO$, 124-19-6; (*S*)-$HOCH_2CH_2CH(OH)CH_3$, 24621-61-2; $TiCl_4$, 7550-45-0; formylcyclohexane, 2043-61-0.

Evaluation of Some Preparations of Trialkoxyphthalic Acid Derivatives

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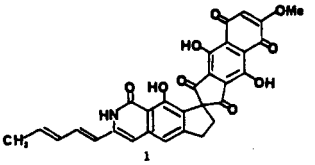
Several approaches to trialkoxyphthalic acid derivatives, potential intermediates in a fredericamycin synthesis, were tested. Sequences based on a Diels-Alder/retro Diels-Alder reaction, a cyanide addition to a quinone, an E1bs oxidation, and an amide-directed ortho-lithiation are discussed in terms of length, yields, convenience, and the versatility of the product of each.

Introduction

Retrosynthetic dissection of the structure of the antitumor antibiotic fredericamycin A (**1**)[1] is likely to lead to consideration of a trialkoxyphthalic acid derivative as a building block. For pursuit of our own synthesis of fredericamycin[2] and analogues which contain the benzindenedione ring system, we required that this key intermediate be obtained easily and in quantity and we preferred that the preparation be inexpensive.



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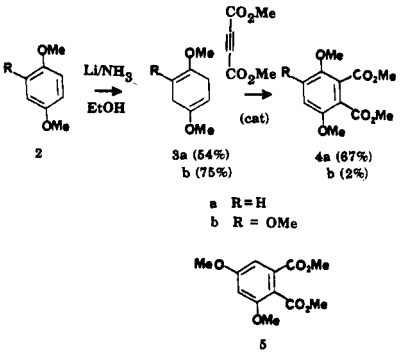
Although a search of the literature revealed only two trialkoxyphthalic acid derivatives,[3] we could imagine various, distinct approaches to members of the class. At this stage, we consider carboxylic ester, nitrile, and aldehydo groups to be potentially useful one-carbon appendages, and we have prepared several compounds which could prove useful for the elaboration of structure **1**. In this paper we describe the advantages and disadvantages of these syntheses as entries to the trialkoxy phthalic acid system.

Scheme I



Results

The Birch Reduction/Diels-Alder Strategy. Phthalic acid derivatives have been prepared by a two-step

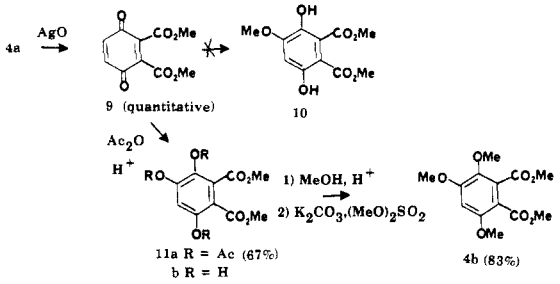
(1) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478.

(2) (a) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181. (b) Parker, K. A.; Breault, G. A. *Tetrahedron Lett.* **1986**, *27*, 3835.

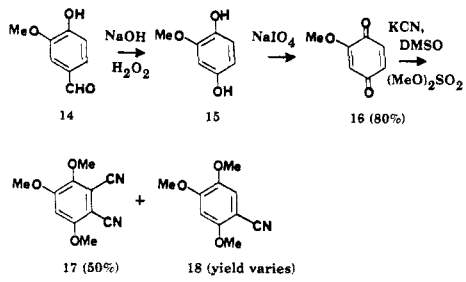
(3) (a) 3,4,6-Trihydroxyphthalonitrile was prepared by Thiele and Gunther (Thiele, J.; Gunther, F. *Justus Liebigs Ann. Chem.* **1906**, *349*, 45). (b) 6-Hydroxy-3,4-dimethoxyphthalic acid was prepared by MacKenzie and Robertson (MacKenzie, J. B. D.; Robertson, A. *J. Chem. Soc.* **1949**, 497).

0022-3263/87/1952-0183$01.50/0

Scheme II

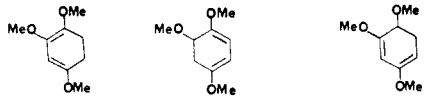


Scheme III



sequence involving Birch reduction of a hydroquinone ether and a one-pot isomerization/Diels–Alder/retro Diels–Alder reaction[4] (e.g., **2a** → **4a**[5]). A very short synthesis based on 1,2,4-trimethoxybenzene (**2b**) was therefore attempted (see Scheme I).

Birch reduction of benzene **2b** with lithium and ethanol in ammonia gave diene **3b** in 75% yield. Treatment of **3b** with dimethyl acetylenedicarboxylate in the presence of dichloromaleic anhydride[4] gave a mixture of trimethoxyphthalate **4b** (2%) and the dimethoxyphthalates **4a** (3%) and **5** (4%). We conclude that isomerization of diene **3b** gives not only 1,2,4-trimethoxy-1,3-cyclohexadiene (**6**), the



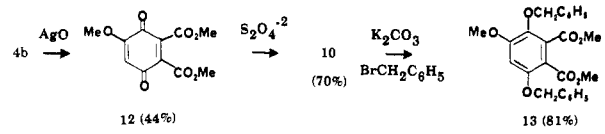
desired precursor to phthalate **4b**, but also 1,4,5-trimethoxy-1,3-cyclohexadiene (**7**), the precursor to **4a**, and 1,3,6-trimethoxy-1,3-cyclohexadiene (**8**), the precursor to **5**. A low recovery of the phthalate mixture (12% total) is not surprising if one considers the instability of dienes **7** and **8** with respect to loss of methanol.

Alternative isomerization methods were explored. The use of tris(triphenylphosphine)chlororhodium as the catalyst[5b] for the one-pot isomerization/Diels–Alder procedure gave a complex mixture of products; none of these was formed in quantities sufficient to warrant identification. Also, an attempt to obtain the desired intermediate diene **6** by isomerization of diene **3b** with potassium amide resulted in the recovery of 1,3-dimethoxybenzene along with some materials which were not identified; this conversion has analogy in the potassium amide induced transformation of 1,2-dimethoxy-1,4-cyclohexadiene to anisole.[6]

Although phthalate **4b** was not prepared efficiently by this simple Diels–Alder strategy, phthalate **4a** is readily available by this same route;[5] the yield of **4a** from **2a** was 36% in our hands. Therefore, we prepared **4a** and attempted to introduce an additional oxygen substituent. Oxidative demethylation[7] of **4a** (see Scheme II) gave quinone **9**;[8] efforts to introduce the additional methoxyl group present in hydoquinone **10** by Michael addition of methanol failed under a variety of conditions (methanol as solvent, 1 equiv of methanol in benzene,[9] zinc chloride catalysis in methanol as solvent[10]).

However, sulfuric acid catalyzed Thiele acylation[11] of quinone **9**[12] proceeded in 65% yield. The triacetoxy phthalate **11a** was deacylated with acidic methanol (see ref. 3a for a similar sequence) to give the trihydroxy compound **11b**.[12] Methylation with dimethyl sulfate and potassium carbonate in acetone gave 3,4,6-trimethoxyphthalate (**4b**, 83% yield from **11a**). By this procedure, then, one of our target compounds was available in five steps.

Because the use of a trialkoxy phthalate in a synthetic scheme might require unmasking of the *p*-hydroxyl groups under mild conditions, we converted phthalate **4b** to the dibenzyl compound **13**. Oxidative demethylation (**4b** → **12**), reduction (**12** → **10**), and alkylation (**10** → **13**) accomplished this transformation in good overall yield. Thus, phthalate **13** is also available by the Diels–Alder/Thiele strategy.



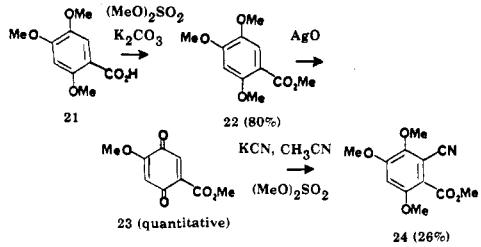
The Cyanide Addition Strategy. The preparation of 3,6-dihydroxyphthalonitrile by double cyanide addition to benzoquinone has been investigated by several groups, apparently with different levels of success.[13] A kinetic study by Guilbault and Kramer[14] showed that the rate of addition of cyanide to benzoquinone increased with the dielectric constant of the solvent; of the solvents studied by these workers, Me_2SO was the most effective for accelerating the addition reaction.

3,6-Dihydroxy-4-methoxyphthalonitrile (**19**) would be the double cyanide addition product from methoxybenzoquinone (**16**).[15] This was prepared from vanillin (**14**) by the Dakin reaction[16] followed by oxidation of the hydroquinone **15** with aqueous sodium periodate (see Scheme III).[17,18]

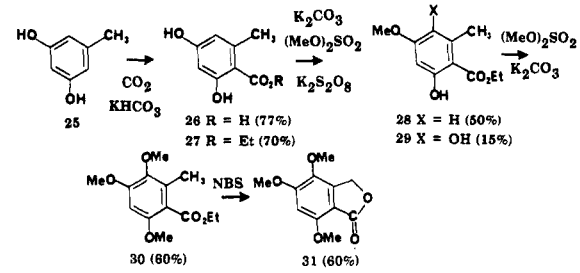
Treatment of methoxybenzoquinone (**16**) with 10 equiv of potassium cyanide in Me_2SO for 43 h followed by quenching with dimethyl sulfate gave the desired 3,4,6-trimethoxyphthalonitrile **17** along with the methylated monocyanide addition product **18** in a ratio of 2:1. We made an attempt to force the double cyanide addition reaction to completion by bubbling oxygen through the

(4) Birch, A. J.; Dastur, K. P. *Tetrahedron Lett.* **1972**, 4195.
(5) (a) Subra Rao, G. S. R.; Sashi Kumar, V. P. *Indian J. Chem., Sect. B* **1979**, 543. (b) Harland, P. A.; Hodge, P. *Synthesis* **1982**, 223.
(6) Birch, A. J. *J. Chem. Soc.* **1947**, 1642.
(7) Synder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.
(8) (a) Ansell, M. E.; Nash, B. W.; Wilson, D. A. *J. Chem. Soc.* **1963**, 3028. (b) Brownbridge, P.; Chan, T.-H. *Tetrahedron Lett.* **1980**, *21*, 3423.
(9) Farina, F.; Valderrama, J. *Synthesis* **1971**, 315.
(10) (a) Knoevenagel, E.; Buchel, C. *Chem. Ber.* **1901**, *34*, 3993. (b) Ashley, J. N. *J. Chem. Soc.* **1937**, 1471.
(11) McOmie, J. F. W., Blatchly *Org. React.* **1972**, *19*, 199–277.
(12) During the course of the work reported here, the conversion of quinone **9** to trihydroxyphthalate **11b** by the Thiele procedure and its conversion to dimethyl 3,6-dihydroxy-4-methoxyphthalate and to quinone **12** appeared. See: Keith D. *Tetrahedron Lett.* **1985**, *26*, 5907.
(13) Allen, C. F. H.; Wilson, C. V. *J. Am. Chem. Soc.* **1941**, *63*, 1756 and references therein. The procedure as described by L. M. Jackman (Jackman, L. M. *Adv. Org. Chem.* **1960**, *2*, 360) was not successful in our hands.
(14) Guilbault, G. G.; Kramer, D. N. *Anal. Chem.* **1965**, *37*, 1395.
(15) (a) Adler, E.; Magnussen, R. *Acta Chem. Scand.* **1959**, *13*, 505. (b) Teuber, H. J.; Rau, W. *Chem. Ber.* **1953**, *86*, 1036.
(16) Surrey, A. R. *Organic Syntheses*; Wiley: New York, 1955; Collect, Vol. III, p 759.
(17) Chatterjee, A.; Ganguly, D.; Sen, R. *Tetrahedron* **1976**, *32*, 2407.
(18) Sworin, M. E. Ph.D. Dissertation, Brown University, 1981.

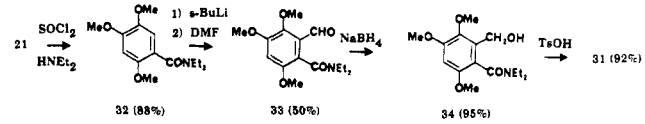
Scheme IV



Scheme V

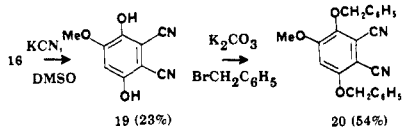


Scheme VI



reaction mixture (in order to oxidize methoxyhydroquinone (**15**) formed in situ from the redox reaction of quinone **16** and the intermediate 2,5-dihydroxy-4-methoxybenzonitrile); however this resulted in the formation of black tarry material. A second attempt to increase conversion involved the use of 20 equiv of potassium cyanide, added in several batches over time to the Me_2SO solution of methoxy benzoquinone. With this procedure we isolated a 50% yield of the double cyanide adduct **17**, uncontaminated by the mono addition product **18**.

By an alternative workup procedure, the intermediate hydroquinone **19** was converted to the dibenzyl ether derivative **20**. Attempts to hydrolyze dinitrile **20** to the



corresponding dicarboxylic acid or imide by the procedure of Thiele and Gunther **20**[3a] resulted only in the recovery of starting dinitrile; on the other hand, heating for extended periods of time led to loss of the material.

A more convenient entry to the trialkoxyphthalic acid derivatives could be attained via a related strategy (Scheme IV). This preparation is based on the commercially available 2,4,5-trimethoxybenzoic acid (**21**). Conversion of acid **21** to its methyl ester **22** was accomplished with dimethyl sulfate in 80% yield. Oxidative demethylation according to the Synder/Rapoport procedure gave ester **23** in quantitative yield. The addition of 1.3 equiv of potassium cyanide to this activated quinone proceeded in acetonitrile; quenching with dimethyl sulfate gave the cyano ester **24** in 26% yield. We have not attempted the hydrolysis of this compound.

The Evernic Acid Strategy. The preparation of trialkoxyphthalic acid derivatives in which the benzylic carbon atoms are in different oxidation states was viewed as potentially advantageous. Such compounds could become available via functionalization of the known ester **30**.[19]

The literature preparation of **30** is based on the Elbs hydroxylation of ethyl evernate (**28**) to hydroquinone **29**, a step which is reported to proceed in only 37% yield. However, evernic acid is commercially available; also it can be prepared from orcinol (**25**).[20,21] Therefore, we repeated the preparation of **30** in the hopes that we could improve the Elbs reaction, thereby making the synthesis useful if not practical.

The literature route to **30** is summarized in Scheme V. The yields shown are ours; experience with the Elbs transformation (**28** → **29**) reinforces the inauspicious claims of others. However, with **30** in hand, we determined to make one of the target compounds. Photolysis of a mixture of ester **30** and 1.25 equiv of NBS followed by heating the crude product with aqueous HCl gave a 60% yield of the trimethoxyphthalide **31**.

The Ortho-Metalation Strategy. A second route to phthalide derivatives was based on ortho-metalation of the diethyl amide of 2,4,5-trimethoxybenzoic acid. Amide **32** was prepared by treatment of acid **21** with thionyl chloride and then diethyl amine (Scheme VI). Ortho-lithiation of the amide[22] followed by quenching with DMF gave a 50% yield of aldehyde **33**. Aldehyde **33** was converted to the simple phthalide **31** by treatment with sodium borohydride (95% yield) followed by cyclization in the presence of toluenesulfonic acid (92%).

Discussion

Of the two routes based on the Diels–Alder/retro Diels–Alder strategy, the first (**2b** → **4b**)is obviously unsatisfactory because of the low yield of product **4b**. The second route (**2a** → **4a** → **9** → **4b**) did afford a reasonable overall yield of the target **4b**. It consists of five steps including one which requires the relatively expensive reagent, AgO.

Of the two routes based on the cyanide addition strategy, the first (Scheme III) suffers from the inefficiency of the cyanide addition reaction; this reaction requires the use of an enormous excess of cyanide in order to get complete reaction, and it necessitates the use of Me_2SO which must be removed by distillation. The second route (Scheme IV) is much more easily carried out and the addition reaction here is fast. However, like the second Diels–Alder approach, this route includes the expensive AgO oxidative demethylation reaction, and the yield of purified cyanide addition product is low.

The last two syntheses produce phthalic acid derivatives in which the benzylic carbons are in different oxidation states. These derivatives have the potential to undergo subsequent reactions with regioselectivity; presumably the compounds discussed above lack this potential. The evernic acid strategy (Scheme V), as it stands, is impractical because of the very low yield in the Elbs oxidation step (**28** → **29**). The ortho-metalation route (Scheme VI), on the other hand, has high yields and is very short. Furthermore, phthalide derivatives from *o*-aldehydobenzoic acid derivatives have been shown to undergo re-

(19) Elix, J. A.; Jayanthi, V. K.; Leznoff, C. C. *Aust. J. Chem.* **1981**, *34*, 1757.

(20) Aghoramurthy, K.; Seshadri, T. R. *Proc. Indian Acad. Sci., Sect. A* **1952**, *35*, 327.

(21) (a) Saraiya, P. R.; Shah, R. C. *Curr. Sci.* **1949**, *18*, 218. (b) Robertson, A.; Robinson, R. *J. Chem. Soc.* **1927**, 2199.

(22) deSilva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802.

giospecific condensation with Michael acceptors.[23]

The ortho metalation procedure therefore, seems to be the most efficacious entry to trialkoxy phthalic acid derivatives, and it affords compounds which should serve as particularly versatile intermediates. The use of the readily available phthalate derivative **33** in the synthesis of quinonoid natural products is being explored and will be reported elsewhere.

Experimental Section

General Procedures. Proton nuclear magnetic resonance spectra were taken on a Varian EM-360 spectrometer and on a Bruker 250 spectrometer. Chemical shifts are reported relative to tetramethylsilane in parts per million. Infrared spectra were taken in $CHCl_3$ on a Perkin-Elmer 681 spectrophotometer, and absorptions are reported in cm^{-1}. High-resolution mass spectra were taken on a Kratos mass spectrometer at 70 eV. Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Packing material for column chromatography was Merck silica gel 60. DMF was dried by storage over 4-Å molecular sieves under nitrogen for 18 h. Other solvents were purified by distillation as follows: THF from Na–benzophenone ketyl, TMEDA from Na, CCl_4 from P_2O_5, and acetone from anhydrous $CaSO_4$.

1,2,4-Trimethoxy-1,4-cyclohexadiene (3b). Ammonia was distilled from Na^0 into a flask containing 1,2,4-trimethoxybenzene (2.00 g, 11.9 mmol) and Et_2O. Next a portion of Li wire was added; this was followed by a portion of EtOH at −33 °C. This procedure was repeated until a total of 388 mg (55.9 mmol) of Li and 3.0 g (65.4 mmol) of EtOH had been added. When the blue color disappeared, the ammonia was evaporated at room temperature. The residue was diluted with H_2O and Et_2O, and the Et_2O layer was dried over $MgSO_4$ and concentrated to afford 1.62 g (80%) of a colorless oil. NMR ($CDCl_3$): δ 2.90 (d, 4 H); 3.54 (s, 3 H); 3.66 (s, 6 H); 4.51 (t, 1 H). IR ($CHCl_3$): 2940, 1705, 1670, 1380, 1150, 980 cm^{-1}.

Dimethyl 3,4,6-Trimethoxyphthalate (4b) and Dimethoxyphthalates 4a and 5. A sample of 1,2,4-trimethoxy-1,4-cyclohexadiene (208 mg, 1.22 mmol), dimethyl acetylenedicarboxylate (267 mg, 1.88 mmol), and dichloromaleic anhydride (3.6 mg, 0.02 mmol) were heated together at 140 °C for 1 h. The crude reaction mixture was subjected to prep TLC with 1:1 hexanes/EtOAc, and seven bands were isolated. Three of these bands were further purified by prep TLC with 1:1 C_6H_6/Et_2O, and the following three compounds were identified: 5.2 mg (2%) of dimethyl 3,4,6-trimethoxyphthalate (**4b**; see alternative preparation from triacetate **11a** for characterization), 8.8 mg (3%) of dimethyl 3,6-dimethoxyphthalate (**4a**),[5b] and 13.8 mg (4.4%) of dimethyl 3,5-dimethoxyphthalate (**5**).[5b]

2,3-Bis(carbomethoxy)-1,4-benzoquinone (9).[8] Dimethyl 3,6-dimethoxyphthalate (**4a**) (161 mg, 0.633 mmol), AgO (314 mg, 2.53 mmol), and acetone (7.5 mL) were mixed together to give a gray suspension. Oxidation was initiated by addition of 6 N HNO_3 (0.71 mL). The reaction was allowed to proceed at 50 °C until all of the AgO was consumed (approximately 10 min). Then it was quenched by the addition of 5 mL of H_2O and 10 mL of $CHCl_3$, and the aqueous layer was extracted 3× with $CHCl_3$. The combined organic solution was dried over $MgSO_4$ and concentrated to yield 140 mg (quantitative yield) of an orange solid, mp 132–134 °C; recrystallization from benzene/pentane gave material with mp 154–155 °C (lit.[8a] mp 155.5–157 °C, lit.[8b] mp 153–154 °C): ^1H NMR ($CDCl_3$, 60 MHz) δ 3.90 (s, 6 H), 6.89 (s, 2 H); IR ($CHCl_3$) 1745, 1690, 1286, 1261, 1231, 1072 cm^{-1}.

Dimethyl 3,4,6-Triacetoxyphthalate (11a).[12] Quinone **9** (39 mg, 0.18 mmol), acetic anhydride (432 mg, 4.24 mmol), and H_2SO_4 (6 mL) were stirred together overnight at 50 °C. Water was then added, and the resulting precipitate was isolated by filtration. Recrystallization from MeOH afforded 44 mg (67%) of a white solid: mp 118–120 °C; NMR ($CDCl_3$) δ 2.25 (s, 9 H), 3.75 (s, 6 H), 7.20 (s, 1 H); IR ($CHCl_3$) 1780, 1730, 1465, 1365, 1190, 1012 cm^{-1}.

Dimethyl 3,4,6-Trihydroxyphthalate (11b).[12] Triacetate **11a** (24.2 mg, 0.0657 mmol) was stirred at reflux with H_2SO_4 (4.1 mL) in MeOH for 6 h. Water was added, and the resulting mixture was concentrated and then extracted 4× with $CHCl_3$. The organic solution was dried over Na_2SO_4 and concentrated to yield material which was used directly in the next step. A sample of this material was purified by flash chromatography (5% MeOH/$CHCl_3$) to give a white solid: NMR ($CDCl_3$) δ 1.58 (br s, 2 H, exch D_2O), 3.86 (s, 3 H), 3.90 (s, 3 H), 6.64 (s, 1 H); 9.72 (s, 1 H, exch D_2O); IR ($CHCl_3$) 1665 (H bonded ester), 1430, 1220 cm^{-1}; M^+ 242.0419 (theory 242.0426).

Dimethyl 3,4,6-Trimethoxyphthalate (4b). The crude trihydroxy compound **11b** (15.9 mg, 0.0657 mmol), K_2CO_3 (54.5 mg, 0.394 mmol), and dimethyl sulfate (66.3 mg, 0.526 mmol) were dissolved in acetone, and the reaction mixture was stirred at reflux overnight. Water was then added, and the mixture was extracted with EtOAc. The EtOAc solution was washed 4× with H_2O to remove excess dimethyl sulfate, then dried over Na_2SO_4, and concentrated to yield 15.5 mg (83%) of a white solid compound. This was recrystallized from Et_2O and MeOH: mp 75.5–76.0 °C; NMR ($CDCl_3$, 250 MHz) δ 3.82 (s, 3 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 6.57 (s, 1 H); IR ($CHCl_3$) 2930, 1725 (ester), 1590, 1440, 1200, 1052 cm^{-1}; M^+ 284.0900 (theory 284.08957).

2,3-Bis(carbomethoxy)-5-methoxy-1,4-benzoquinone (12).[12] Compound **4b** (15.3 mg, 0.0538 mmol) and AgO (26.7 mg, 0.215 mmol) were dissolved in acetone. To this was added 64 mL of 6 N HNO_3. After being stirred for 45 min, the reaction mixture was quenched by the addition of H_2O and $CHCl_3$. The $CHCl_3$ layer was concentrated to yield 13.0 mg of crude product. Flash chromatography (2:1 hexanes/EtOAc) afforded 6.0 mg (44%) of pure material: NMR ($CDCl_3$, 250 MHz) δ 3.87 (s, 3 H), 3.92 (s, 6 H), 6.02 (s, 1 H); IR ($CHCl_3$) 1740, 1605, 1430, 1280, 1260 cm^{-1}.

Dimethyl 3,6-Dihydroxy-4-methoxyphthalate (10).[12] Quinone **12** (66.5 mg, 0.261 mmol) was dissolved in 2 mL of Et_2O, and to this was added $Na_2S_2O_4$ (91.0 mg, 0.523 mmol) dissolved in 1 mL of H_2O. The mixture was heated to 50 °C with occasional shaking. The Et_2O layer was separated and washed with saturated salt solution. The organic layer was dried over Na_2SO_4 and concentrated to yield 46.6 mg (70%) of a white solid. Flash chromatography with 1:1 hexanes/EtOAc gave pure product with mp 145–147 °C NMR ($CDCl_3$, 60 MHz) δ 3.98 (br, s, 9 H), 6.57 (s, 1 H); IR ($CHCl_3$) 3540, 2940, 1730, 1665, 1030 cm^{-1}; M^+ 256.0592 (theory 256.0583).

Dimethyl 3,6-Bis(benzyloxy)-4-methoxyphthalate (13). Hydroquinone **10** (21.6 mg, .0843 mmol) and K_2CO_3 (34.9 mg, 0.253 mmol) were dissolved in 3 mL of acetone. To this was added benzyl bromide (43.3 mg, 0.253 mmol), and the reaction mixture was stirred at reflux for 24 h. The mixture was diluted with H_2O and extracted 3× with Et_2O. The Et_2O solution was dried over Na_2SO_4 and concentrated to give 35 mg (94%) of yellow oil. Flash chromatography gave 30 mg (81%) of pure material: NMR ($CDCl_3$, 60 MHz) δ 3.90 (br s, 9 H), 5.03 (s, 2 H), 5.19 (s, 2 H), 6.65 (s, 1 H), 7.48 br s, 10 H); IR ($CHCl_3$) 2950, 1726, 1586, 1435, 1332, 1045 cm^{-1}; M^+ 436.1513 (theory 436.1521).

2-Methoxy-1,4-benzoquinone (16).[15] Sodium periodate (447 mg, 2.1 mL) was dissolved in 15 mL of H_2O, and to this was added 2-methoxyhydroquinone (**15**, 86.5 mg, 0.617 mmol). The solution turned clear yellow and was stirred for 1 h. It was extracted with CH_2Cl_2, and the resulting organic solution was dried over $MgSO_4$ and concentrated to yield 68.0 mg (80%) of a bright yellow solid: mp 142–144 °C. (lit.[15a] 142–146 °C, lit.[15b] 139–140 °C); NMR ($CDCl_3$) δ 3.93 (s, 3 H), 6.06 (s, 1 H), 6.82 (s, 2 H); IR ($CHCl_3$) 1675, 1650, 1590, 1230, 1095 cm^{-1}.

3,4,6-Trimethoxy-1,2-benzenedicarbonitrile (17). Methoxyquinone (**16**, 28.8 mg, 0.208 mmol) and KCN (136 mg, 2.08 mmol) were dissolved in Me_2SO, and the reaction mixture was stirred for 4 h. Over the next 6 h, additional portions of KCN totaling 136 mg (2.08 mmol) were added. The reaction mixture was allowed to stir overnight, and the Me_2SO was distilled off. The residue was next dissolved in acetone, and to this were added K_2CO_3 (115 mg, 0.832 mmol) and dimethyl sulfate (629 mg, 5.0 mmol). The reaction mixture stirred overnight, water and Et_2O were added, and then the Et_2O layer was washed several times with H_2O to remove traces of dimethyl sulfate. The Et_2O solution was dried over $MgSO_4$ and then evaporated in vacuo to yield 11.4

(23) Kraus, G. A.; Cho, H.; Crawley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439 and references therein.

mg (50%) of a white solid. Crystallization from EtOAc/hexanes gave white crystals: mp 196–196.5 °C; NMR ($CDCl_3$, 60 MHz) δ 4.00 (s, 9 H), 6.69 (s, 1 H); IR ($CHCl_3$) 3040, 2220, 1586, 1490, 1355, 1073 cm^{-1}; M^+ 218.0683 (theory 218.0691).

3,4,6-Trimethoxy-1,2-benzenedicarbonitrile (17) and 2,4,5-Trimethoxybenzonitrile (18). A sample of 2-methoxy-1,4-benzoquinone (23.6 mg, 0.171 mmol) and KCN (111 mg, 1.71 mmol) were dissolved in Me_2SO and stirred at room temperature for 43 h. The Me_2SO was distilled off, and K_2CO_3 (118.0 mg, 0.854 mmol), dimethyl sulfate (107.7 mg, 0.854 mmol), and acetone (3 mL) were added. This was stirred overnight, then diluted with H_2O, and extracted 4× with Et_2O. The organic layers were evaporated in vacuo, and NMR examination of this mixture revealed a 2:1 ratio of dicyano to monocyano compound. A sample of 3,4,6-trimethoxybenzonitrile was isolated by flash chromatography with 1:1 hexane/EtOAc: NMR ($CDCl_3$, 60 MHz) δ 3.85 (s, 3 H); 3.96 (s, 6 H); 6.50 (s, 1 H); 6.96 (s, 1 H); IR ($CHCl_3$) 2960, 2215, 1609, 1515, 1280, 1023 cm^{-1}; M^+ 193.0742 (theory 193.0738). For spectroscopic data of dinitrile **17**, see the preferred experimental procedure above.

3,6-Dihydroxy-4-methoxy-1,2-benzenedicarbonitrile (19). A sample of 2-methoxybenzoquinone (74.4 mg, 0.539 mmol) and KCN (77.2 mg, 1.18 mmol) were dissolved in Me_2SO. This stirred for 1 h; then the Me_2SO was distilled off, and a few drops of 1 N HCl were added to the residue. The H_2O was evaporated in vacuo. Then the product was dissolved in CH_3CN, coated onto silica gel, and subjected to flash chromatography (MeOH/$CHCl_3$ 1:8) to give 17 mg (23%) of product: NMR (CD_3CN, 60 MHz) δ 3.90 (s, 3 H), 6.78 (s, 1 H); IR (KBr) 3200 br, 2230, 1495, 1270 cm^{-1}; M^+ 190.0364 (theory 190.0378).

3,6-Bis(benzyloxy)-4-methoxy-1,2-benzenedicarbonitrile (20). A sample of hydroquinone **19** (12.4 mg, 0.0898 mmol) was dissolved in 1 mL of acetone and 0.5 mL of THF. To this was added K_2CO_3 (37.2 mg, 0.269 mmol) and the reaction mixture stirred for 35 min. Benzyl bromide (33.8 mg, 0.198 mmol) was added dropwise, and the reaction mixture was allowed to stir overnight. Then Et_2O and 1 N HCl were added, and the aqueous layer was extracted 3× with Et_2O. The Et_2O solution was dried over $MgSO_4$ and then concentrated. Flash chromatography (3:2 hex/EtOAc) afforded 15.5 mg (54%) of a white solid; mp 156 °C; NMR ($CDCl_3$, 60 MHz) δ 3.92 (s, 3 H), 5.13 (s, 2 H) 5.26 (s, 2 H), 6.70 (s, 1 H), 7.40 (s, 10 H); IR ($CHCl_3$) 3000, 2220, 1585, 1480, 1440, 1060 cm^{-1}; M^+ 370.1314 (theory 370.1317).

Methyl 2,4,5-Trimethoxybenzoate (22). 2,4,5-Trimethoxybenzoic acid (**21**, 435 mg, 2.05 mmol) was dissolved in acetone, and to this was added K_2CO_3 (368 mg, 2.66 mmol). Dimethyl sulfate (335 mg, 2.66 mmol) was added by syringe. The reaction mixture was stirred at reflux for 3 h, then diluted with H_2O, and extracted 4× with Et_2O. The Et_2O solution was dried over $MgSO_4$ and concentrated to afford an off-white solid. Recrystallization from MeOH gave 371 mg (80%) of product: mp 90–91 °C; NMR ($CDCl_3$, 60 MHz) δ 3.89 (m, 12 H), 6.50 (s, 1 H), 7.38 (s, 1 H); IR ($CHCl_3$) 2940, 1705, 1510, 1250, 1200, 1025 cm^{-1}; M^+ 226.0855 (theory 226.0841).

2-Methoxy-5-carbomethoxy-1,4-benzoquinone (23). Methyl 2,4,5-trimethoxybenzoate (**22**; 39.7 mg, 0.187 mmol) and AgO (92.7 mg, 0.748 mmol) were dissolved in 2 mL of acetone. Oxidation was initiated by addition of 0.166 mL of 6 N HNO_3. The reaction was allowed to stir at 50 °C until the grey suspension disappeared and the color became yellow (about 4 min). The reaction was quenched immediately with H_2O and $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and concentrated to give a quantitative yield of crude material, 36 mg: mp 98–100 °C; NMR ($CDCl_3$) δ 3.90 (s, 3 H), 3.97 (s, 3 H), 6.02 (s, 1 H), 7.04 (s, 1 H); IR ($CHCl_3$) 2940, 1740, 1680, 1650, 1600, 1165 cm^{-1}. This product is unstable to chromatography and was used directly in the next step.

Methyl 2-Cyano-3,4,6-trimethoxybenzoate (24). Quinone **23** (38.0 mg, 0.208 mmol) and KCN (17.7 mg, 0.271 mmol) were dissolved in CH_3CN. The reaction mixture was stirred at room temperature overnight and then concentrated. To the residue, K_2CO_3 (93.6 mg, 0.677 mmol), dimethyl sulfate (78.7 mg, 0.624 mmol), and 4 mL of acetone were added, and the resulting mixture was stirred at reflux for 3 h. The reaction mixture was cooled, and H_2O and Et_2O were added. The organic layer was dried over Na_2SO_4 and concentrated to give 33.4 mg of **24**, (64% overall crude yield of **24** from **23**), mp 139–140 °C. The product was chromatographed with 1:1 hexanes/EtOAc to give 13.7 mg (26% yield) of clean **24** from **23**: NMR ($CHCl_3$) δ 3.86 (s, 3 H), 3.92 (s, 9 H), 6.69 (s, 1 H); IR ($CDCl_3$) 3000, 2220, 1725, 1340, 1260, 1070, 1025 cm^{-1}; M^+ 251.0797 (theory 251.0793).

3,5,6-Trimethoxyphthalide (31). A mixture of ester **24** (50 mg, 0.20 mmol) and recrystallized NBS (45 mg, 0.25 mmol) in 2.5 mL of dry CCl_4 was stirred at reflux during irradiation for 2 h. Then succinimide was filtered from the cooled reaction mixture, and the filtrate was concentrated. To the residue was added 2.5 mL of 2.5 M HCl. The resultant solution was stirred at reflux for 12 h, then cooled, diluted with H_2O, and extracted (2×) with EtOAc. The combined organic solution was washed with 5% $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. The crude product was subjected to flash chromatography with EtOAc/hexanes (1/1) to afford 27 mg (60%) of a white solid. Recrystallization from Et_2O–hexanes gave a shiny white solid, mp 134–5 °C. The IR and NMR data are identical with those of a sample prepared by the alternative procedure described below.

***N,N*-Diethyl-2,4,5-trimethoxybenzamide (32).** To thionyl chloride (4.2 mL, 48 mmol), cooled to 0 °C, was added 2,4,5-trimethoxybenzoic acid (5.0 g, 24 mmol). The reaction mixture was stirred at reflux under an atmosphere of N_2 for 4 h. Excess thionyl chloride was removed by distillation to yield a white solid. This was added to *N,N*-diethylamine (5 mL, 48 mmol) in 5 mL of dry benzene cooled to 0 °C. The reaction mixture was allowed to stir overnight at room temperature under an atmosphere of N_2. After cooling, the reaction mixture was washed with dilute HCl 2× and with brine, dried with $MgSO_4$, and concentrated to a light brown oil. The crude product was purified by flash chromatography with EtOAc/hexanes (1:1) to afford 5.7 g (88%) of a white solid. Recrystallization from EtOAc/hexanes have a white crystalline solid, mp 73–4°C; IR ($CHCl_3$) 3005, 2985, 1600, 1500, 1270, 1025 cm^{-1}; NMR (250 MHz; $CDCl_3$) δ 1.02 (t, J = 7 Hz, 3 H), 1.21 (t, J = 7 Hz, 3 H), 3.16 (q, J = 7 Hz, 2 H), 3.45–3.60 (br m, 2 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 6.48 (s, 1 H), 6.73 (s, 1 H); M^+ 267.1454 (theory 267.1470).

***N,N*-Diethyl-2,4,5-trimethoxy-6-formylbenzamide (33).** A solution of benzamide **32** (1.67 g, 6.24 mmol) and freshly distilled TMEDA (1.9 mL, 12.5 mmol) in 10 mL of anhydrous THF was cooled to −78 °C under an atmosphere of N_2. To the solution at −78 °C was added *sec*-BuLi (8.9 mL of a 1.4 M solution in cyclohexane, 12.5 mmol). After the reaction mixture was stirred at −78 °C for 1 h, DMF (previously dried over molecular sieves, 1.0 mL, 13.0 mmol) was added. Stirring at −78 °C for 1 h was followed by removal of the cooling bath. The reaction mixture was allowed to stir at room temperature for 12 h. After acidification of the reaction mixture, the aqueous and organic layers were separated. The aqueous solution was extracted 3× with EtOAc. The combined organic solution was washed with brine, then dried over Na_2SO_4, and concentrated to a yellow oil. The crude product was purified by flash chromatography; elution with EtOAc afforded 92 mg (50%) of a solid. Recrystallization from EtOAc/hexanes afforded colorless needles, mp 92–94 °C; IR ($CHCl_3$) 2990, 1685, 1610, 1585, 1265, 1030 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 1.28 (t, J = 7 Hz, 3 H), 3.06 (q, J = 7 Hz, 2 H), 3.38–3.50 (m, 1 H), 3.65–3.79 (m, 1 H), 3.80 (s, 3 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 6.72 (s, 1 H), 10.34 (s, 1 H); M^+ 295.1405 (theory 295.1419).

***N,N*-Diethyl-6-(hydroxymethyl)-2,4,5-trimethoxybenzamide (34).** To a solution of formylbenzamide **33** (32 mg, 0.11 mmol) in 4 mL of absolute EtOH was added 5.0 mg (0.125 mmol) of $NaBH_4$ (95%). Stirring of the reaction mixture at room temperature was continued for $^1/_2$ h. The reaction was quenched by the addition of dilute HOAc and concentrated. The resulting aqueous solution was extracted twice with CH_2Cl_2. The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated to an oil. The reaction product was purified via a chromatotron with EtOAc to afford 31 mg (95%) of a solid. Recrystallization from EtOAc/hexanes afforded a white crystalline solid, mp, 117-8°C; IR ($CHCl_3$) 3415, 3010, 1590, 1200, 1035 cm^{-1}; NMR (250 MHz;$CDCl_3$) δ 1.01 (t, J = 7 Hz, 3 H), 1.23 (t, J = 7 Hz, 3 H) 3.11–3.21 (m, 2 H), 3.37 (br s, exchanges with D_2O, 1 H), 3.55 (q, J = 7 Hz, 2 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 3.87 (s, 3 H), 4.31 (d of ABq, J = 12 Hz, 1 H), 4.65 (d of ABq, J = 12 Hz, 1 H), 6.44 (s, 1 H); M^+ 297.1562 (theory 297.1576).

3,5,6-Trimethoxyphthalide (31). A solution of benzamide **31** (100 mg, 0.34 mmol) and a catalytic amount of TsOH in 2.5 mL of anhydrous THF was stirred at reflux overnight under an atmosphere of N_2; then the cooled reaction mixture was washed with saturated $NaHCO_3$ (2×) and with brine, dried over Na_2SO_4, and concentrated to a solid. Recrystallization in Et_2O/hexanes afforded a shiny white solid, 70 mg (92%), mp 134-135 °C; IR ($CHCl_3$) 1745, 1605, 1500, 1050 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 3.96 (s, 3 H), 5.20 (s, 2 H), 6.46 (s, 1 H); M^+ 224.0690 (theory 224.0684).

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General Scope of 1,3-Dioxolanation of α,β-Unsaturated Aldehydes with 1,2-Bis((trimethylsilyl)oxy)ethane and Trimethylsilyl Trifluoromethanesulfonate

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1,3-Dioxolanation of α,β-unsaturated aldehydes with 1,2-bis((trimethylsilyl)oxy)ethane in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst has been systematically investigated. These silylated reagents readily acetalize aliphatic, highly conjugated aliphatic, and aromatic enals. Under the mild, aprotic conditions of the reaction, olefins do not rearrange or isomerize, and the acid-sensitive propionyloxy, (tetrahydropyranyl)oxy, and vinyl ether moieties are relatively stable. Aromatic bromide, furan, thiophene, and nitro functionalities are also inert. The only limitation found is in the case of 4-(dimethylamino)cinnamaldehyde, which did not afford a detectable amount of the corresponding dioxolane.

The 1,3-dioxolane moiety is one of the most frequently used protecting groups for carbonyl compounds.[1] For our work in the total synthesis of natural products, we required an efficient method to convert α,β-unsaturated aldehydes to the corresponding 1,3-dioxolanes under mild conditions with reagents compatible with various functional groups. A trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) catalyzed dioxolanation of ketones using 1,2-bis((trimethylsilyl)oxy)ethane (BTSE) under aprotic conditions has been reported by Noyori et al.[2] To our knowledge, no systematic study on the use of these reagents to protect α,β-unsaturated aldehydes has been reported. Herein, we disclose the scope and limitations of the procedure for the protection of α,β-unsaturated aldehydes. Our results should be of significance to the synthetic community.

Results and Discussion

Addition of an enal to a solution of BTSE (1.2 equiv) and a catalytic amount (0.01 equiv) of Me_3SiOTf in dichloromethane at −78 °C provided the corresponding unsaturated dioxolane, generally in good-to-excellent yield (Scheme I). The reaction proceeded rapidly (3-4 h) for most substrates. Both acyclic (e.g., **1a**) and cyclic enals (e.g., **1b**, with the C=C double bond endocyclic) gave the corresponding acetals readily. Neither the terminal C=C double bond in **1a** nor the isopropenylic C=C double bond in **1b** shifted to the more thermodynamically stable position under the reaction conditions. This is consistent with results obtained in a β,γ-enone system reported previously.[2]

Elongation of the conjugated system of enals by one C=C double bond, as in **1c**, or with a phenyl group, as in **1d**, did not significantly influence the reaction rate. Both of these substrates gave the corresponding dioxolanes in excellent yield within 4 h at −78 °C. Extensive conjugation of the enal moiety with additional C=C double bonds as in **1e** did not substantially retard acetalization.

The acid-sensitive allylic propionyloxy and (tetrahydropyranyl)oxy groups in **1f** and **1g**, respectively, were relatively inert toward the acetalization reagents at −78 °C. However, loss of the tetrahydropyranyl (THP) group in **2g** occurred when the reaction mixture was warmed to room temperature. In order to obtain a respectable yield of **2g**, it was necessary to react **1g** with only a slight excess (1.05 equiv) of BTSE at −78 °C for 24 h. Note that attempted acetalization of **1g** by typical methods using ethylene glycol in the presence of various catalysts, such as *p*-toluenesulfonic acid, pyridinium *p*-toluenesulfonate,[3]

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