Two Practical Syntheses of Sterically Congested Benzophenones†,‡

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Two efficient syntheses of the sterically congested tetraortho-substituted benzophenone portion of balanol **1** (a potent PKC inhibitor) in a protected form are described. Ortho lithiation reactions are employed for the preparation of the required 1,2,3-trisubstituted aryl aldehydes (**11** and **26**) and for their subsequent coupling reactions (with **6** and **23**, respectively). The resulting carbinol intermediates [**12**, **27** and **35** (from cross coupling of **11** and **23**)] were then manipulated to the corresponding benzophenonecarboxylic acids **2**, **31**, and **39**, respectively. This chemistry is amenable to large scale synthesis, and multigram quantities of final products have been prepared.

Introduction

Protein kinase C (PKC) belongs to a family of serine/threonine specific protein kinases which is believed to play a pivotal role in signal transduction pathways[1] and has been implicated in several disease state processes.[2] Possible applications of inhibitors of PKC as therapeutic agents encompass a wide spectrum and may include those such as cancer, asthma, HIV infection, rheumatoid arthritus, diabetic complications, and central nervous system disorders.[2]

Recently, our search for novel and potent protein kinase C inhibitors resulted in the discovery of balanol **1** (IC_{50} around 4–9 nM in assays against human PKC enzymes α, β-I, β-II, γ, δ, ϵ, and η) a metabolite produced by the fungus *Verticillium balanoides* which was collected from *Pinus palustris* needle litter.[3]

The structure elucidation of balanol **1**[3] was closely followed by total synthesis[4] and this allowed the preparation of a series of structural analogs[5] for biological evaluation. The accumulated SAR results established the critical importance of the benzophenone portion of balanol for efficacy.[5] As a result, we required an efficient general synthesis of suitably protected tetraortho-substituted benzophenones (such as that shown in Figure 1) which would be amenable to the preparation of bulk material and also be adaptable for the synthesis of further analogs to aid the rapid evaluation of this series of compounds.

The original synthesis of protected benzophenone acid **2** (Figure 2)[4] commenced with 3-(benzyloxy)benzyl alcohol

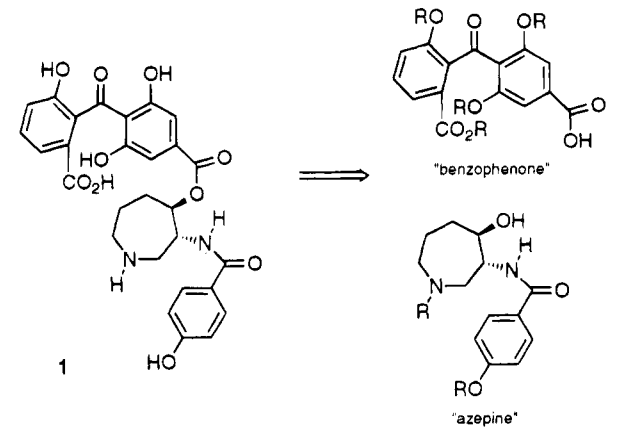

Figure 1. Retrosynthetic analysis of balanol **1** where R is some suitable protecting group, for example, Bn or MOM.

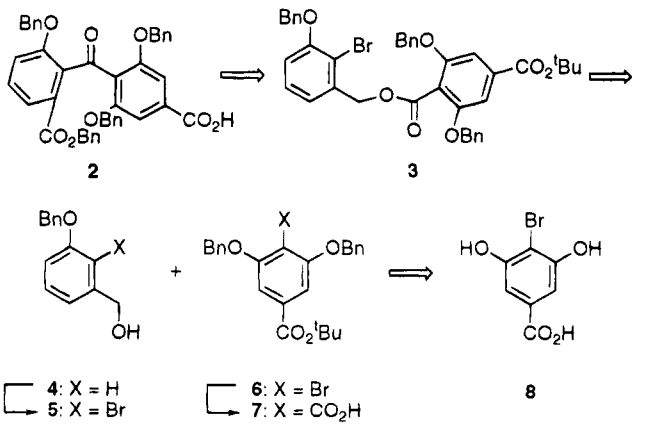

Figure 2. Original retrosynthetic disconnection of benzophenone **2** (see ref 4).

(**4**) and 4-bromo-3,5-dihydroxybenzoic acid (**8**). The key step involved an anionic homo-Fries rearrangement (Figure 2)[4] for the assembly of the required tetraortho-substituted benzophenone. Although this chemistry proved successful for the preparation of gram quantities of benzophenone **2**, this was only after considerable effort. In particular, some chemical reactions did not scale well, and yields fell below an acceptable level. For example, transformation of aryl bromide **6** to the corresponding carboxylic acid **7** (see Figure 2) was a poor yielding conversion (<35% on a 1 kg scale). Also, for the Fries rearragement to proceed efficiently, bromo ester **3** had

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(1) Nishizuka, Y. *Nature* **1988**, *334*, 661. Parker, P. J.; Kour, G.; Marais, R. M.; Mitchell, F.; Pears, C.; Schaap, D.; Stabel, S.; Webster, C. *Mol Cell. Endocrinol.* **1989**, *65*, 1. Stabel, S.; Parker, P. J. *Pharmacol. Ther.* **1991**, *51*, 71.

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(5) Manuscripts in preparation.

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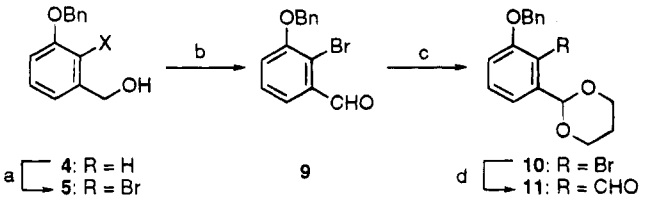
Scheme 1[a]



[a] Reagents: (a) see ref 4; *n*-BuLi, PhMe, −20 °C; $BrF_2CH_2CH_2F_2Br$ (55%); (b) TEMPO, THF, NaBr, NaOCl, 0 °C (90%); (c) $HO(CH_2)_3OH$, *p*-TSA, PhMe, reflux (96%); (d) *n*-BuLi, THF, −78 °C; DMF (79%).

to be pure in order to avoid problems associated with incomplete reaction. Under these conditions, although addition of further reagent (*n*-BuLi) was found to effect complete conversion, the product tended to be contaminated and the resulting side products were extremely difficult to remove. In addition, several time-consuming and tedious chromatographic purifications were necessary. These limitations required an improved process for the preparation of benzophenone acid **2** that would be more amenable to the requirements of large scale synthesis.

It is noteworthy that various prior attempts to assemble the benzophenone unit directly *via* Stille[6] type couplings proved fruitless, presumably due to the nature of the highly sterically constrained tetraortho-substituted arrangement.[4] This necessitated the investigation of another method of construction of the biaryl ketone.

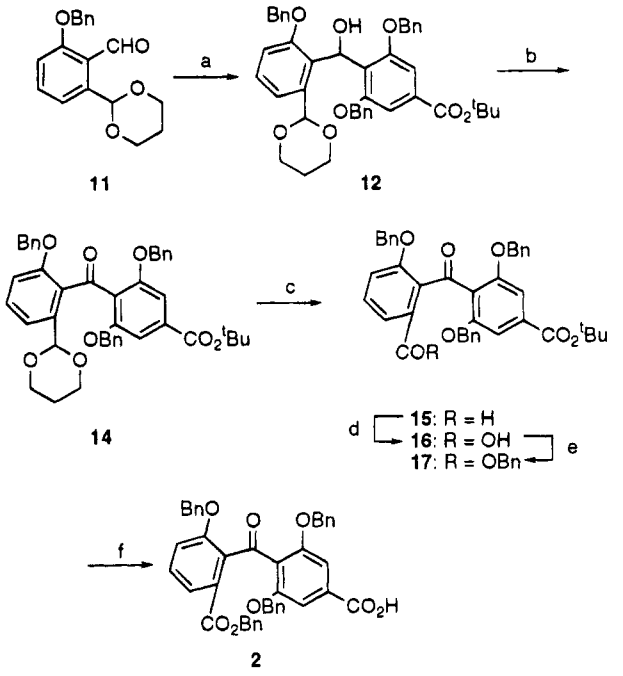
Described in this paper are two alternative syntheses of suitably protected forms of the basic benzophenone skeleton of balanol **1** which have been used for the preparation of multigram amounts of final analog products for biological evaluation.

Results and Discussion

Our first approach was a variation on the original route and takes advantage of the same readily prepared starting materials, aryl bromide **6** (prepared in three steps from 4-bromo-3,5-dihydroxybenzoic acid (**8**)) and bromo alcohol **5** (prepared by *ortho*-lithiation[7] and bromination of 3-(benzyloxy)benzyl alcohol (**4**)).[4] Bromo alcohol **5** was oxidized to aldehyde **9** with TEMPO[8] (90%) and protected as cyclic ketal **10** (1,3-propanediol, catalytic *p*-TSA, toluene, reflux: 96%) (Scheme 1). The required 1,2,3-trisubstituted aldehyde **11** could then be generated in 79% yield by bromine−lithium exchange (of **10**) with *n*-butyllithium followed by a quench with DMF. No chromatography was necessary for the synthesis of any of these intermediates, all of which were purified by simple recrystallization of crude reaction mixtures. All reactions are readily amenable to scale up and have been performed without incident on a several hundred gram scale.

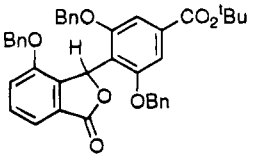
Coupling (see Scheme 2) of aryl bromide **6** with aldehyde **11** proceeded (^{n}BuLi, THF, −78 °C) to provide carbinol **12** in moderate yield (61% after chromatography). Attempted oxidation of **12** with either Jones reagent or chromium trioxide (under conditions which are

Scheme 2[a]



[a] Reagents: (a) **6**, *n*-BuLi, THF, −78 °C (61%); (b) MnO_2, CH_2Cl_2 (96%); (c) *p*-TSA, acetone, H_2O, reflux (95%); (d) $NaClO_2$, H_2NSO_3H, MeCN, H_2O; (e) BnBr, K_2CO_3, DMF (97% over two steps); (f) see ref 4; quinoline, 205 °C (68%).

suitable for substrates containing acid labile groups[9]) afforded lactone **13** in quantitative crude yield.



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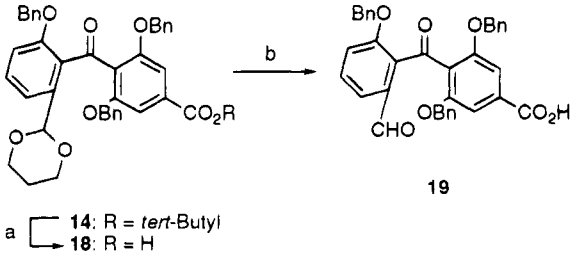
The ketone **14** could, however, be generated by oxidation of alcohol **12** with PDC (with NaOAc buffer), TPAP[10] (87%), or more conveniently with manganese dioxide (96%).

The resulting benzophenone **14** was then deprotected by *p*-TSA-catalyzed acetal hydrolysis to afford the corresponding aldehyde **15** in 95% yield. This intermediate was common with the original synthetic route[4] and thereby constitutes a convergent synthesis of benzophenone acid **2**. Although aldehyde **15** was previously oxidized[4] with tetrabutylammonium permanganate, oxidation with sodium chlorite[11] to carboxylic acid **16** proved to be more convenient. Benzylation (to **17**) and *tert*-butyl deprotection as before[4] provided the desired benzophenone acid **2**.

Unfortunately, the removal of the *tert*-butyl protecting group in the presence of benzyl ester (as for **17**) was an inconvenient step which involved a thermolysis (quinoline, 205 °C) and a chromatographic purification and proceeded only in moderate yield (68%). Alternative reaction conditions (formic acid, TFA, basic hydrolysis) were nonselective.[4] This reaction step could be avoided,

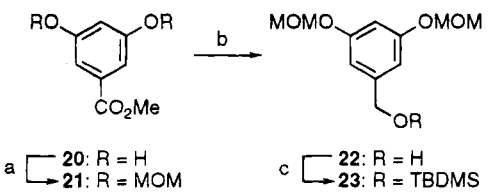
(6) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634.
(7) Review in: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(8) For example, see: Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, 5029 and ref 7 therein.
(9) Flatt, S. J.; Fleet, G. W. J.; Taylor, B. J. *Synthesis* **1979**, 815.
(10) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
(11) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.

Scheme 3[a]



[a] Reagents: (a) NaOH, THF–MeOH, H_2O, reflux (95%); (b) *p*-TSA, acetone, H_2O, reflux (90%).

Scheme 4[a]



[a] Reagents: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 (67%); (b) $LiAlH_4$, THF; (c) TBDMSCl, imidazole, CH_2Cl_2 (87% over two steps).

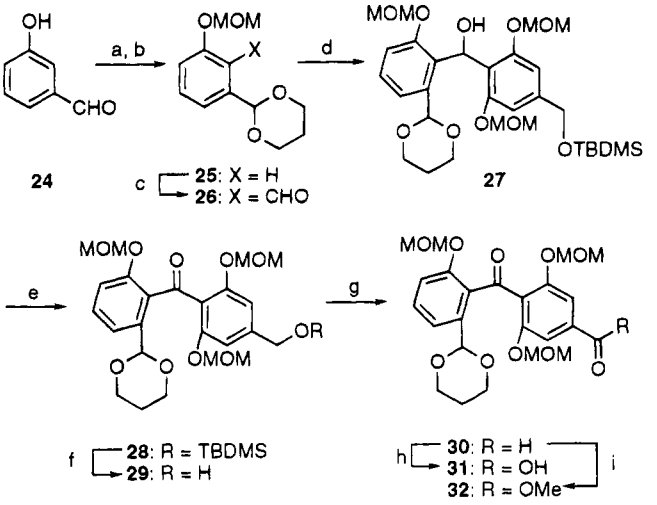
however, by performing the deprotection step prior to formation of the benzyl ester. For example, NaOH hydrolysis of *tert*-butyl ester **14** (see Scheme 3) provided acid **18** (95%) which could also be subjected to *p*-TSA-catalyzed acetal hydrolysis (90%) to furnish aldehyde–acid **19**. Both of these intermediates **18** and **19** are suitable for coupling and have been successfully transformed to analogs of balanol following manipulation of the acetal or aldehyde functionality.[5]

Although this process was able to readily provide the basic benzophenone **14** on a several hundred gram scale, this chemistry also had some limitations for bulk synthesis. In particular, there are two low-temperature (−78 °C) reactions (including a low-temperature addition of the aryl lithiate of **6** and one chromatographic purification (during the preparation of **12**)). As an alternative approach to overcome some of these obstacles (and also to provide additional benzophenone analogs for the continuing accumulation of SAR data) the following chemistry was developed.

The bis MOM aryl ether **23** was prepared from methyl 3,5-dihydroxybenzoate **20** in three steps (Scheme 4) by standard chemical procedures. Thus, **20** was treated with MOMCl to provide bis MOM ether **21** which was reduced to alcohol **22** with $LiAlH_4$ and then protected as the TBDMS ether **23**.

In addition, 3-hydroxybenzaldehyde (**24**) was converted to the corresponding acetal with 1,3-propanediol (Scheme 5) catalyzed by alumina[12] and protected as the MOM ether **25**.[13] *Ortho*-lithiation[7] (^{n}BuLi, cyclohexane, ambient temperature) of **25**[13] was followed by formylation with DMF to provide a quantitative crude yield of 1,2,3-trisubstituted aryl aldehyde **26** (<10% contamination with 1,2,4-substituted regioisomer). This material was most conveniently used without further purification. The bis-MOM ether **23** was subjected to standard *ortho*-lithiation conditions[7] (^{n}BuLi, THF, 0 °C) and allowed to react (Scheme 5) with crude aldehyde **26** to provide carbinol **27** in modest yield (53% after chromatography).

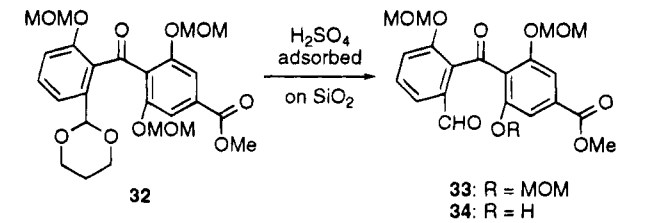
Scheme 5[a]



[a] Reagents: (a) $HO(CH_2)_3OH$, Al_2O_3, PhMe, reflux (81%); (b) MOMCl, NaH, THF–DMF (96%); (c) *n*-BuLi, C_6H_{12}, room temperature; DMF; (d) **23**, *n*-BuLi, THF, 0 °C (54% over two steps); (e) MnO_2, CH_2Cl_2 (100%); (f) TBAF, THF (93%); (g) MnO_2 (84%); (h) $NaClO_2$, H_2O_2, NaH_2PO_4, $MeCN–H_2O$ (79%); (i) KOH, I_2, MeOH, 0 °C (90%).

Oxidation [TPAP (87%) or MnO_2 (100%)] to benzophenone **28** was followed by deprotection with TBAF (93%) to alcohol **29** and two-step oxidation (MnO_2, then $NaClO_2$, NaH_2PO_4, H_2O_2, $MeCN–H_2O$:[14] 68% over two steps) to carboxylic acid **31**. Alternatively, methyl ester **32** could be generated from aldehyde **30** in a one-step oxidation (KOH, I_2, MeOH, 0 °C).[15]

This ester intermediate **32** allowed the investigation of the selective deprotection of the acetal moiety in the presence of the MOM groups. The best conditions found were to employ aqueous sulfuric acid adsorbed on silica gel.[16]

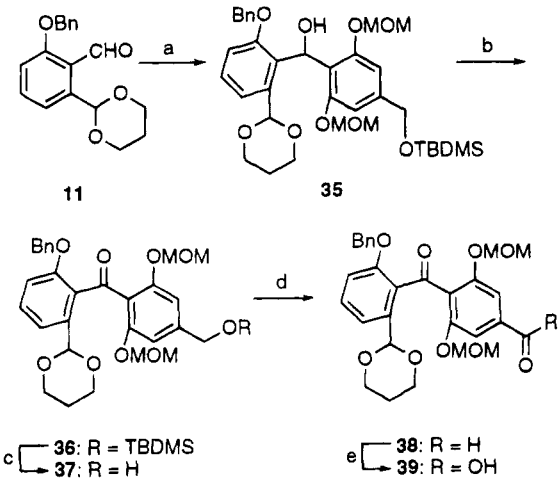


When 5% H_2SO_4 on silica was employed a *ca.* 3:1 mixture of aldehyde **33** and mixed aldehyde–phenol **34** (in which a single MOM group has also been cleaved) was isolated. Although reaction conditions for the completely selective formation of aldehyde **33** could not be determined a longer reaction time (or more conveniently use of 18% H_2SO_4 on silica) gave pure **34** in 63% yield after crystallization. This material **34** may be reprotected as the MOM ether **33** or reacted in such a way as to provide differentially functionalized benzophenone (and balanol) analogs.[5]

A differentially protected analog **39** could also be prepared (Scheme 6) by reaction of the lithiate of bis MOM aryl ether **23** with (benzyloxy)aryl aldehyde **11** to afford carbinol **35** in 73% yield. Oxidation (MnO_2, 93%)

(12) Kamitori, Y.; Hojo, M.; Masuda, R.; Yoshida, T. *Tetrahedron Lett.* **1985**, 4767.
(13) Winkle, M. W.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101.
(14) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.
(15) Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, 4329.
(16) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.

Scheme 6[a]



[a] Reagents: (a) **23**, *n*-BuLi, THF, 0 °C (73%); (b) MnO_2, CH_2Cl_2 (93%); (c) TBAF, THF (88%); (d) MnO_2, CH_2Cl_2 (97%); (e) $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN–H_2O (98%).

to benzophenone **36**, alcohol deprotection to **37** (TBAF; 88%), and two-step oxidation [MnO_2 (97%), followed by $NaClO_2$, NaH_2PO_4, H_2O_2, H_2O[14] (98%)] gave the corresponding carboxylic acid **39**.

The synthetic routes to the basic benzophenone skeletons **31** and **39** have been employed to supply tens of grams of benzophenone product to date and offer the advantage of avoiding all low-temperature reaction conditions.

Conclusions

In summary, we have been able to outline the syntheses of suitably protected derivatives of the benzophenone portion of balanol. This chemistry has been shown to be amenable to large scale synthesis and has supplied the benzyl-protected benzophenone **14** (by the chemistry described in Scheme 2) and the MOM-protected benzophenones **31** and **39** in multigram amounts for the synthesis of a plethora of balanol analogs. In addition, it is believed that the chemistry described here is general and should be applicable for the synthesis of other sterically congested tetraortho-substituted benzophenones.

Selective hydrolysis conditions for the removal of the acetal in the presence of MOM protecting groups was investigated for methyl ester **32** where the clean removal of acetal and one MOM group was observed (18% H_2SO_4 adsorbed on silica) to provide **34** (where one phenolic group has now been differentiated). This chemistry (in accompaniment with the synthesis of mixed benzyl and MOM protected benzophenones, as for **39**) has also enabled the preparation of differentially functionalized benzophenone and balanol analogs.[5]

Experimental Section

Unless otherwise stated, all reactions were carried out under a dry nitrogen atmosphere using commercially available anhydrous solvents.

3-(Benzyloxy)-2-bromobenzyl alcohol (5) and **1,1-dimethylethyl 3,5-bis(benzyloxy)-4-bromobenzoate (6)** were prepared according to the procedure described in ref 4.

3-(Benzyloxy)-2-bromobenzaldehyde (9). 3-(Benzyloxy)-2-bromobenzyl alcohol (**5**)[4] (251 g, 0.86 mol) was dissolved in THF (300 mL) and sodium bromide (13.2 g, 0.128 mol) added. The reaction mixture was cooled to 0 °C and TEMPO (0.67 g, 4.28 mmol) added followed by a freshly prepared (0 °C) solution of sodium bicarbonate (10.8 g, 0.128 mol) in commercial Chlorox bleach (1 L). This was stirred rapidly at 0 °C for 3 h at which time sodium sulfite was added. The precipitated solids were dissolved with the addition of deionized water. The organics were separated and the aqueous layer extracted (2×) with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated. The residue was cooled in an ice bath, and the precipitated solids were collected by filtration to afford the title compound **9** (224 g, 90%) as a white solid: mp 124–6 °C (EtOAc); ^1H NMR ($CDCl_3$) 5.21 (2H, s), 7.16 (1H, dd, J = 1.53, 9.24 Hz), 7.32–7.58 (7H, m), 10.48 (1H, s); IR (KBr) 1564, 1679 cm^{-1}. Anal. Calcd for $C_{14}H_{11}O_2Br$: C, 57.76; H, 3.81. Found: C, 57.68; H, 3.77.

2-[2-Bromo-3-(benzyloxy)phenyl]-1,3-dioxane (10). The aldehyde **9** (215 g, 0.738 mol) was combined in toluene (200 mL) with 1,3-propanediol (107 mL, 1.48 mol) and pTSA·H_2O (1.6 g) and heated at the reflux temperature with azeotropic removal of water *via* a Dean-Stark trap. After 1.5 h the reaction mixture was cooled and washed with saturated sodium bicarbonate and brine. The organics were separated, dried ($MgSO_4$), and evaporated. The residue was crystallized from methanol to afford the title compound **10** as a white solid (248 g, 96%): mp 73–4 °C; ^1H NMR ($CDCl_3$) 1.45 (1H, d, J = 13.6 Hz), 2.18–2.35 (1H, m), 4.01–4.14 (2H, m), 4.25–4.33 (2H, m), 5.16 (2H, s), 5.87 (1H, s), 6.93 (1H, d, J = 7.3 Hz), 7.21–7.52 (7H, m); ^{13}C NMR ($CDCl_3$) 26.31, 68.18, 71.64, 101.66, 113.62, 114.82, 120.85, 127.58, 128.48, 128.70, 129.14, 137.13, 139.77, 155.40; IR (KBr) 1569 cm^{-1}. Anal. Calcd for $C_{17}H_{17}O_3Br$: C, 58.47; H, 4.91. Found: C, 58.52; H, 4.76.

2-[2-Formyl-3-(benzyloxy)phenyl]-1,3-dioxane (11). ^{n}BuLi (236.2 mL of a 1.6 M solution in hexanes, 0.378 mol) was added dropwise to a solution of **6** (120 g, 0.344 mol) in dry THF (600 mL) at −78 °C. The temperature was maintained <−60 °C during this period, and stirring was continued for an additional 15 min after the final addition. Anhydrous DMF (532.2 mL, 6.87 mol) was then added dropwise at such a rate as to maintain the temperature below −60 °C. The resulting solution was stirred at −65 °C for 4 h and allowed to slowly warm to ambient temperature and stirred overnight (16 h). The reaction was quenched upon addition of saturated ammonium chloride solution, and the solvents were removed *in vacuo*. The residue was partitioned between ethyl acetate and brine. The organics were sequentially washed with brine and water several times, dried ($MgSO_4$), and evaporated to a solid which was recrystallized from ethyl acetate–hexanes to afford the title compound **11** (80.7 g, 79%) as a white crystalline solid: mp 85–7 °C; ^1H NMR ($CDCl_3$) 1.41–1.47 (1H, m), 2.16–2.30 (1H, m), 4.02–4.11 (2H, m), 4.21–4.30 (2H, m), 5.20 (2H, s), 6.31 (1H, s), 7.05 (1H, dd, J = 2.44, 6.83 Hz), 7.34–7.54 (7H, m), 10.70 (1H, s); ^{13}C NMR ($CDCl_3$) 26.44, 68.18, 71.42, 98.29, 114.15, 119.71, 123.11, 127.86, 128.83, 129.30, 135.42, 136.61, 140.72, 161.94, 192.57; IR (KBr) 1585, 1687 cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.43; H, 6.26.

1,1-Dimethylethyl 4-[[2-(Benzyloxy)-6-(1,6-dioxanyl)-phenyl]hydroxymethyl]-3,5-bis(benzyloxy)benzoate (12). ^{n}BuLi (77.86 mL of 2.5 M solution in hexanes, 0.195 mol) was added dropwise to a −70 °C solution of aryl bromide **6** (83.1 g, 0.177 mol) in anhydrous THF (800 mL) at a rate to maintain the internal temperature <−65 °C. After the final addition the mixture was stirred for a further 10 min, whereupon the purple solution was added quickly *via* cannula to a −70 °C solution of aldehyde **11** (44.0 g, 0.147 mol) in dry THF (800 mL). The resulting yellow reaction mixture was stirred at this temperature overnight at which time solid ammonium chloride was added and the mixture allowed to warm to ambient temperature. Deionized water (700 mL) was then added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the combined organics were washed with brine, dried ($MgSO_4$), and evaporated to afford a yellow oil which was chromatographed (SiO_2, 15% ethyl acetate–hexanes). The title compound **12** was isolated as a white foam (62.23 g, 61%): ^1H NMR ($CDCl_3$) 1.23–1.36 (1H, m), 1.55 (9H, br s), 2.06–2.27 (1H, m), 3.60–3.88 (2H, m),

4.02–4.18 (2H, m), 4.80 (2H, AB quartet, J_{AB} = 12.09 Hz), 4.89 (4H, br s), 5.26–5.32 (1H, m), 6.00 (1H, s), 6.75 (2H, t, J = 7.75 Hz), 6.89 (2H, d, J = 7.14 Hz), 7.09–7.28 (16H, m), 7.38 (1H, d, J = 7.75 Hz); IR (KBr) 1583, 1708, 3488 cm^{-1}. Anal. Calcd for $C_{43}H_{44}O_8$: C, 74.98; H, 6.44. Found: C, 74.76; H, 6.24.

Oxidation of 12 with Jones Reagent. Jones reagent (3 drops) was added to a 0 °C solution of alcohol **12** (33 mg, 0.0479 mmol) in acetone. After 15 min 2-propanol (2 drops) was added and the solution diluted further with acetone and filtered through Celite. The filtrates were evaporated and the residue partitioned between diethyl ether and 10% sodium bicarbonate. The organics were separated, washed with brine, dried ($MgSO_4$), and evaporated to provide lactone **13** as a gum (31 mg, 100%) which solidified upon standing. Data for **13**: ^1H NMR ($CDCl_3$) 1.61 (9H, s), 4.62–5.04 (2H, AB quartet, J = 11.36 Hz), 4.80 (2H, pseudo d, J = 13.25 Hz), 4.87–5.00 (2H, AB quartet, J = 11.60 Hz), 6.81–6.90 (4H, m), 7.02 (1H, d, J = 7.88 Hz), 7.13–7.33 (16H, m); ^{13}C NMR ($CDCl_3$) 28.74, 70.40, 70.77, 71.44, 73.78, 82.07, 106.78, 106.87, 116.20, 116.45, 117.75, 127.85, 127.97, 128.08, 128.53, 128.59, 128.84, 128.88, 129.08, 129.80,130.48, 134.37, 136.02, 136.55, 136.99, 138.51, 153.38, 158.44, 158.90, 165.67, 171.84; IR (KBr) 1586, 1713, 1761 cm^{-1}. Anal. Calcd for $C_{40}H_{36}O_7$: C, 76.42; H, 5.77. Found: C, 76.57; H, 5.98.

1,1-Dimethylethyl 4-[2-(Benzyloxy)-6-(1,6-dioxanyl)-benzoyl]-3,5-bis(benzyloxy)benzoate (14). Manganese dioxide (250 g) was added in portions to a stirred solution of **12** (62.2 g, 0.090 mol) in methylene chloride (1.5 L). The reaction mixture was allowed to stir overnight at ambient temperature at which time the catalyst was removed by filtration through Celite. The pad was washed with further methylene chloride, and the filtrates were evaporated to afford the title ketone **14** as a white foam (59.81 g, 96%): mp (MeOH) 134–5 °C; ^1H NMR ($CDCl_3$) 1.33 (1H, d, J = 13.2 Hz), 1.55 (9H, s), 2.10–2.28 (1H, m), 3.76–3.88 (2H, m), 4.10–4.18 (2H, m), 4.64 (2H, s), 4.82 (4H, s), 5.72 (1H, s), 6.79 (1H, d, J = 7.02 Hz), 6.86 (1H, d, J = 7.82 Hz), 7.08–7.28 (16H, m), 7.40 (1H, t, J = 8.00 Hz), 7.50 (1H, d, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) 25.40, 27.75, 66.96, 69.55, 70.03, 80.96, 99.08, 106.25, 112.18, 119.21, 124.64, 126.73, 127.16, 127.22, 127.37, 127.73, 127.89, 129.85, 130.61, 133.51, 135.61, 136.05, 138.91, 156.01, 156.42, 164.51, 194.16; IR (KBr) 1584, 1674, 1711 cm^{-1}. Anal. Calcd for $C_{43}H_{42}O_8$: C, 75.20; H, 6.16. Found: C, 75.17; H, 6.04.

1,1-Dimethylethyl 3,5-Bis(benzyloxy)-4-[6-(benzyloxy)-2-formylbenzoyl]benzoate (15). Benzophenone **14** (58.0 g, 0.084 mol) was dissolved in a mixture of acetone (270 mL) and deionized water (30 mL). A catalytic amount of pTSA·H_2O was added, and the mixture was refluxed for 3 h. The solution was basified with saturated sodium bicarbonate, and the acetone was removed *in vacuo*. The aqueous layer was extracted with ethyl acetate, and the organics were dried ($MgSO_4$) and evaporated. The residue was crystallized from methanol to afford the title aldehyde **15** (50.48 g, 95%) as a white solid: mp 108–10 °C; ^1H NMR ($CDCl_3$) 1.64 (9H, s), 4.76 (2H, s), 4.78 (4H, s), 6.81–7.44 (20H, m); ^{13}C NMR (d_6-DMSO) 28.12, 70.13, 70.58, 81.62, 106.68, 118.22, 120.01, 123.96, 127.74, 128.20, 128.36, 128.46, 128.62, 132.50, 132.85, 134.26, 135.78, 136.52, 137.97, 156.65, 157.06, 164.54, 191.62, 193.55; IR (KBr) 1584, 1665, 1709 cm^{-1}. Anal. Calcd for $C_{40}H_{36}O_7$: C, 76.42; H, 5.77. Found: C, 76.18; H, 5.79.

1,1-Dimethylethyl 4-[6-(Benzyloxy)-2-(benzyloxycarbonyl)benzoyl]-3,5-bis(benzyloxy)benzoate (17).[4] A solution of sulfamic acid (4.01 g, 0.041 mol) in deionized water (50 mL) was added to a solution of aldehyde **15** (20.0 g, 0.032 mol) in acetonitrile (300 mL) at ambient temperature. After 5 min a solution of sodium chlorite (4.82 g of 80%, 0.043 mol) in deionized water (50 mL) was also added dropwise. Once complete the reaction mixture was stirred for 30 min. The solvent was removed *in vacuo*, and the aqueous layer was extracted several times with ethyl acetate. The organics were combined, dried ($MgSO_4$), and evaporated to afford the acid **16** (20.5 g) as white solid which was used in the next step without further purification. The crude carboxylic acid **16** (20.5 g, 0.32 mol) was dissolved in anhydrous DMF (500 mL), and potassium carbonate (13.2 g, 0.095 mol) and benzyl bromide (4.54 mL, 0.38 mol) were added sequentially. The reaction mixture was allowed to stir overnight, and the solvent was removed *in vacuo*. Deionized water was added and the aqueous layer extracted with ethyl acetate. The organic layer was washed with brine and water, dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, 9:1 hexane–ethyl acetate) to afford the title ester **17** (22.7 g, 97%) as a yellow viscous oil which was identical to material prepared previously.[4]

3,5-Bis(benzyloxy)-4-[2-(benzyloxy)-6-(1,6-dioxanyl)-benzoyl]benzoic Acid (18). A mixture of acetal **14** (10.0 g, 14.6 mmol) and 1 M sodium hydroxide (44 mL, 44 mmol) in THF–water (2:1; 150 mL total volume) was heated to 60 °C overnight. The crude reaction mixture was allowed to cool and concentrated. The residue was partitioned between water (150 mL) and ethyl acetate (200 mL). The pH of the aqueous layer was adjusted to pH 1 with 1 N hydrochloric acid and the organic layer separated. The aqueous layer was re-extracted with ethyl acetate, and the combined organics were dried ($MgSO_4$) and evaporated to give the title compound **18** as a pale yellow solid: mp 176–177 °C; ^1H NMR ($CDCl_3$) 1.36 (1H, d, J = 14.28 Hz), 2.19–2.24 (1H, m), 3.80–3.88 (2H, m), 4.13–4.18 (2H, m), 4.64 (2H, s), 4.82 (4H, bs), 5.70 (1H, s), 6.77–7.51 (20H, m); ^{13}C NMR (d_6-DMSO) 25.71, 67.13, 69.60, 70.06, 99.09, 106.78, 113.34, 119.60, 124.56, 127.27, 127.90, 127.97, 128.39, 128.58, 129.84, 131.18, 133.55, 136.50, 136.87, 139.00, 156.80, 167.03, 193.83; IR (KBr) 1588, 1673, 1719, 3144, 3418 cm^{-1}. Anal. Calcd for $C_{39}H_{34}O_8$: C, 74.27; H, 5.43. Found: C, 74.14; H, 5.68.

4-[2-(Formyl)-6-(benzyloxy)benzoyl]-3,5-bis(benzyloxy)-benzoic Acid (19). Acetal **18** (0.5 g, 0.79 mmol) was dissolved in acetone–water (10:1; 11 mL total volume) containing a catalytic amount of pTSA·H_2O and heated at reflux for 2 h. The reaction mixture was allowed to cool and neutralized with saturated sodium bicarbonate solution. The acetone was removed *in vacuo* and the aqueous layer extracted with ethyl acetate. The combined organics were dried ($MgSO_4$) and evaporated. The residue was chromatographed (SiO_2, 1% methanol–methylene chloride) to provide the title compound **19** as a pale orange foam (0.41 g, 90%). An analytical sample was prepared by crystallization from methanol: mp 201–204 °C; ^1H NMR ($CDCl_3$) 4.76 (2H, s), 4.80 (4H, s), 6.83–7.48 (20H, m), 9.87 (1H, s); IR (KBr) 1581, 1688, 3370, 3459 cm^{-1}. Anal. Calcd for $C_{36}H_{28}O_7$: C, 75.51; H, 4.93. Found: C, 75.14; H, 4.96.

3,5-Bis(methoxymethoxy)-1-[[(*tert*-butyldimethylsilyl)oxy]methyl]benzene (23). MOMCl (29.8 mL, 0.393 mol) was added dropwise to an ice-cooled solution of diisopropylethylamine (77.7 mL, 0.446 mol) and methyl 3,5-dihydroxybenzoate (**20**) (30.0 g, 0.178 mol) in dry methyene chloride (200 mL). After the final addition the reaction mixture was allowed to warm to ambient temperature and stir overnight. The solution was poured into deionized water and the organic layer separated and washed with 10% aqueous copper sulfate solution, dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, 15:1–9:1 hexane–ethyl acetate, gradient elution) to afford the major product methyl 3,5-bis(methoxymethoxy)benzoate (**21**) (34.5 g, 75%) as a clear colorless oil. This material was used without further purification: ^1H NMR ($CDCl_3$) 3.48 (6H, s), 3.90 (3H, s), 5.19 (4H, s), 6.91 (1H, t, J = 2.25 Hz), 7.36 (2H, d, J = 2.16 Hz). A solution of ester **21** (36.0 g, 0.14 mol) in anhydrous THF (200 mL) was added dropwise to a stirred solution of lithium aluminum hydride (183 mL of a 1.0 M solution in THF, 0.183 mol). The reaction mixture was stirred at ambient temperature for 2 h whereupon deionized water (8 mL), 15% aqueous NaOH (8 mL) and deionized water (28 mL) were sequentially added dropwise. After the final addition stirring was continued for 2 h and the mixture was filtered. The solid was washed with ethyl acetate and the filtrate was evaporated to provide alcohol **22** as a clear colorless oil (32 g, 100%). This material was not purified but was carried to the next step. Data for **22**: ^1H NMR ($CDCl_3$) 3.45 (6H, s), 4.61 (1H, br s), 5.12 (4H, s), 6.62 (1H, t, J = 2.20 Hz), 6.70 (2H, d, J = 2.15 Hz). A solution of *tert*-butyldimethylsilyl chloride (29.8 g, 0.198 mol) in anhydrous methylene chloride (100 mL) was added to a stirred mixture of imidazole (13.46 g, 0.198 mol) and alcohol

22 (41.0 g, 0.180 mol) in dry methylene chloride. After being stirred overnight the reaction mixture was poured into deionized water. The organic layer was separated, washed with 10% aqueous copper sulfate solution and brine, dried ($MgSO_4$), and evaporated. The residue was filtered through a column of silica (SiO_2, 10:1 hexane–ethyl acetate elution) to provide the title compound **23** (53.7 g, 87%) as a colorless oil: ^1H NMR ($CDCl_3$) 0.10 (6H, s), 0.95 (9H, s), 3.48 (6H, s), 4.70 (2H, s), 5.18 (4H, s), 6.61 (1H, t, J = 2.26 Hz), 6.70 (2H, d, J = 2.14 Hz); IR (neat) 1560 cm^{-1}. Anal. Calcd for $C_{17}H_{30}O_5Si$: C, 59.61; H, 8.83. Found: C, 59.63; H, 8.75.

1-[[2-(1,6-Dioxanyl)-6-(methoxymethoxy)phenyl]hydroxymethyl]-2,6-bis(methoxymethoxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]benzene (27). ^{n}BuLi (10.9 mL of a 1.6 M solution in hexanes, 17.5 mmol) was added dropwise to a stirred solution of **25**[13] (3.56 g, 15.9 mmol) in anhydrous cyclohexane at ambient temperature. The mixture (which gummed up) was stirred for 15 min whereupon dry DMF (3.69 mL, 47.6 mmol) was then added dropwise and stirring was continued for an additional 15 min. The reaction was quenched upon addition of brine and diluted with ethyl acetate. The organic layer was separated and washed with brine and deionized water and then dried ($MgSO_4$) and evaporated to a light yellow gum. This aldehyde **26** (4.0 g, 100%) was used without further purification. ^{n}BuLi (6.80 mL of a 1.6 M solution in hexanes, 10.9 mmol) was added dropwise to a solution of **23** (3.4 g, 9.93 mmol) in dry THF at 0 °C over a 5 min period. Stirring was then continued for 15 min whereupon this solution was added *via* cannula to a solution of the above-prepared crude aldehyde **26** (2.63 g, 10.4 mmol) in anhydrous THF at 0 °C. The light yellow solution was then allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with brine and diluted with ethyl acetate. The layers were separated and the aqueous extracted with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, 2:1 hexanes–ethyl acetate) to afford the title alcohol **27** as a gum (2.5 g, 41%). Impure aldehyde **26** (500 mg) was also recovered. Data for **27**: ^1H NMR ($CDCl_3$) 0.08 (6H, s), 0.90 (9H, s), 1.38–1.46 (1H, m), 2.17–2.32 (1H, m), 3.10 (3H, s), 3.24 (6H, s), 3.90–4.07 (2H, m), 4.18–4.31 (2H, m), 4.63 (2H, s), 4.80 (1H, d, J = 6.9 Hz), 4.92 (2H, s), 5.05 (4H, s), 6.31 (1H, s), 6.62 (1H, d, J = 6.8 Hz), 6.76 (2H, s), 6.98 (1H, d, J = 7.69 Hz), 7.16 (1H, t, J = 8.06 Hz), 7.42 (1H, d, J = 7.14 Hz); ^{13}C NMR ($CDCl_3$) −5.74, 17.86, 25.40, 55.05, 55.37, 64.16, 66.03, 66.96, 93.56, 94.20, 98.84, 105.89, 114.14, 119.20, 126.96, 130.12, 137.83, 141.97, 153.88, 155.34.

2′-(1,6-Dioxanyl)-6′-(methoxymethoxy)-2,6-bis(methoxymethoxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]benzophenone (28). Manganese dioxide (5.35 g, 61.5 mmol) was added in portions to a solution of alcohol **27** (2.44 g, 4.10 mmol) in dry methylene chloride. The resulting mixture was stirred at ambient temperature for 16 h. The catalyst was removed by filtration through Celite, and the filtrates were evaporated to provide the title compound **28** as a colorless gum: ^1H NMR ($CDCl_3$) 0.07 (6H, s), 0.92 (9H, s), 1.31–1.41 (1H, m), 2.10–2.30 (1H, m), 3.11 (3H, s), 3.24 (6H, s), 3.81–3.89 (2H, m), 4.15–4.18 (2H, m), 4.67 (2H, s), 4.89 (4H, s), 4.99 (6H, s), 5.62 (1H, s), 6.77 (2H, s), 7.03 (1H, d, J = 8.25 Hz), 7.30 (1H, t, J = 8.06 Hz), 7.44 (1H, d, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) −5.75, 17.87, 25.38, 55.16, 55.39, 64.13, 66.96, 93.75, 94.00, 99.07, 105.29, 114.44, 119.78, 120.70, 130.08, 131.34, 138.20, 145.65, 153.57, 155.61, 194.44; IR (neat) 1606, 1677 cm^{-1}. Anal. Calcd for $C_{30}H_{44}O_{10}Si \cdot 0.3H_2O$: C, 60.24; H, 7.51. Found: C, 59.89; H, 7.56.

3,5-Bis(methoxymethoxy)-4-[2-(methoxymethoxy)-6-(1,6-dioxanyl)benzoyl]benzyl Alcohol (29). Tetrabutylammonium fluoride (4.86 mL of a 1.0 M solution in THF, 4.86 mmol) was added dropwise to a solution of **28** (2.40 g, 4.05 mmol) in anhydrous THF and the mixture allowed to stir at ambient temperature for 1 h. Brine was added, and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine. All the aqueous extracts were combined and back-extracted with methylene chloride. The organic extracts were similarly combined, dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, 2:1 ethyl acetate–hexanes) to provide the title compound **29** as a white solid: mp 84–6 °C; ^1H NMR ($CDCl_3$) 1.40 (1H, br d, J = 13.61 Hz), 1.77 (1H, br t, J = 5.50 Hz), 2.13–2.34 (1H, m), 3.14 (3H, s) 3.26 (6H, s), 3.84–3.95 (2H, m), 4.20 (2H, dd, J = 5.01, 10.63 Hz), 4.66 (2H, d, J = 5.01 Hz), 4.90 (2H, s), 5.03 (6H, s), 5.64 (1H, s), 6.80 (2H, s), 7.02 (1H, d, J = 8.20 Hz), 7.34 (1H, t, J = 7.94 Hz), 7.46 (1H, d, J = 7.14 Hz); IR (KBr) 1607, 1661, 3488 cm^{-1}. Anal. Calcd for $C_{24}H_{30}O_{10}$: C, 60.24; H, 6.32. Found: C, 59.95; H, 6.59.

3,5-Bis(methoxymethoxy)-4-[2-(methoxymethoxy)-6-(1,6-dioxanyl)benzoyl]benzaldehyde (30). Manganese dioxide (12 g) was added in portions to a stirred solution of alcohol **29** (14.1 g, 29.5 mmol) in dry methylene chloride. The reaction mixture was stirred for 2 days, and the catalyst was removed by filtration through Celite. The catalyst was washed with further methylene chloride, and the filtrates were evaporated to yield the title compound **30** as a white foam (12.2 g, 84%) which was used without further purification: ^1H NMR ($CDCl_3$) 1.41 (1H, br d, J = 12.15 Hz), 2.15–2.34 (1H, m), 3.07 (3H, s), 3.27 (6H, s), 3.87–3.99 (2H, m), 4.22 (1H, dd, J = 5.06, 10.74 Hz), 4.88 (2H, s), 5.31 (6H, s), 5.71 (1H, s), 7.03 (1H, d, J = 8.24 Hz), 7.31 (2H, s), 7.38 (1H, t, J = 8.12 Hz), 7.51 (1H, d, J = 7.14 Hz), 9.92 (1H, s).

3,5-Bis(methoxymethoxy)-4-(2-methoxymethoxy)-6-(1,6-dioxanyl)benzoic Acid (31). A solution of aldehyde **30** (12.2 g, 24.8 mmol) and NaH_2PO_4 (1.04 g, 8.67 mmol) in acetonitrile–deionized water (160 mL total volume; 6:1 v/v) was cooled in an ice bath. Hydrogen peroxide (3 mL of a 30% solution in water) was added followed by solid sodium chlorite (4.4 g of 80%). This mixture was stirred for 1 h, and the solvent was removed *in vacuo*. Deionized water was added and the precipitated solid collected by filtration. This was dried *in vacuo* to give the title acid **31** (9.11 g). The filtrates were extracted with methylene chloride, dried ($MgSO_4$), and evaporated. The residue was crystallized from ethyl acetate–hexanes to provide further acid **31** (0.8 g). These solid materials were combined to give a total yield of 9.91 g (79%): mp 152–3 °C (EtOAc–hexanes); ^1H NMR ($CDCl_3$) 1.40 (1H, br d, J = 12.1 Hz), 2.18–2.35 (1H, m), 3.09 (3H, s), 3.25 (6H, s), 3.82–3.98 (2H, m), 4.22 (2H, dd, J = 4.64, 11.1 Hz), 4.88 (2H, s), 5.09 (4H, s), 5.70 (1H, s), 7.04 (1H, d, J = 8.24), 7.40 (1H, t, J = 8.05 Hz), 7.46–7.55 (3H, m); ^{13}C NMR ($CDCl_3$) 26.34, 56.22, 56.69, 68.06, 94.61, 94.84, 99.89, 110.26, 115.30, 121.12, 127.93, 130.70, 132.04, 132.18, 139.84, 155.00, 155.98, 171.09, 195.11; IR (KBr) 1592, 1687, 3540 cm^{-1}. Anal. Calcd for $C_{24}H_{28}O_{11}$: C, 58.53; H, 5.73. Found: C, 58.30; H, 5.73.

Methyl 3,5-Bis(methoxymethoxy)-4-[2-(methoxymethoxy)-6-(1,6-dioxanyl)benzoyl]benzoate (32). A 0 °C solution of potassium hydroxide (0.53 g, 9.50 mmol) in methanol was added dropwise to a 0 °C solution of aldehyde **30** (1.80 g, 3.65 mmol) in methanol. This was followed by the dropwise addition of a solution of iodine (1.20 g, 4.75 mmol) in methanol (precooled to 0 °C) and allowed to stir for 1 h. The sequential addition of KOH and iodine was repeated two more times. After the final addition the reaction mixture was warmed to ambient temperature and allowed to stir for 1 h. At this time 1 N potassium hydrogen sulfate was added dropwise until neutral. The solvents were removed *in vacuo* (bath temperature <30 °C) and the residue partitioned between ethyl acetate and brine. The organics were separated and washed with aqueous sodium thiosulfate, dried ($MgSO_4$), and evaporated to afford the title ester **32** as a white solid (1.66 g, 90%) which was used without further purification. An analytical sample could be prepared by chromatography (SiO_2, 8:5 hexane–ethyl acetate): mp 104–5 °C; ^1H NMR ($CDCl_3$) 1.30 (1H, br d, J = 12.15 Hz), 2.03–2.23 (1H, m), 2.96 (3H, s), 3.13 (6H, s), 3.76–3.85 (2H, m), 3.80 (3H, s), 4.05–4.13 (2H, m), 4.77 (2H, s), 5.00 (4H, s), 5.58 (1H, s), 6.93 (1H, d, J = 8.2 Hz), 7.25 (1H, t, J = 8.1 Hz), 7.35–7.42 (3H, m); ^{13}C NMR ($CDCl_3$) 26.21, 52.84, 56.00, 56.35, 60.79, 94.31, 95.01, 99.89, 107.42, 114.94, 120.81, 126.92, 130.08, 131.78, 132.85, 139.87, 154.88, 155.94, 166.24, 195.01; IR (KBr) 1587, 1670, 1727 cm^{-1}. Anal. Calcd for $C_{25}H_{30}O_{11}$: C, 59.28; H, 5.97. Found: C, 59.38; H, 6.05.

Methyl 4-[6-Formyl-2-(methoxymethoxy)benzoyl]-5-hydroxy-3-(methoxymethoxy)benzoate (34). A solution of

ester (1.65 g, 3.26 mmol) in methylene chloride was added to a stirred mixture of 18% sulfuric acid adsorbed on silica[16] (*ca.* 12 g). The reaction mixture was stirred at ambient temperature for 10 h, whereupon solid sodium carbonate was added and the resulting mixture stirred for 5 min and filtered through a sintered funnel. The solid material was washed with methylene chloride, and the filtrates were evaporated. The residue was crystallized from diethyl ether to afford the title compound **34** (1.12 g, 63%) as a light yellow solid: mp 106–8 °C; ^{1}H NMR ($CDCl_3$) 3.01 (3H, s), 3.31 (3H, s), 3.91 (3H, s), 4.70 (2H, s), 5.10 (2H, s), 7.06 (1H, s), 7.38–7.61 (4H, m), 9.93 (1H, s), 12.66 (1H, s); IR (KBr) 1566, 1631, 1717 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_9$: C, 59.41; H, 4.98. Found: C, 59.71; H, 5.06.

If the reaction is run for shorter periods of time or a lower concentration of sulfuric acid is employed varying amounts of **methyl 4-[6-formyl-2-(methoxymethoxy)benzoyl]-3,5-bis-(methoxymethoxy)benzoate (33)** may be isolated as a gum: ^{1}H NMR ($CDCl_3$) 3.10 (3H, s), 3.27 (6H, s), 3.91 (3H, s), 4.92 (2H, s), 5.10 (4H, s), 7.31 (1H, d, J = 8.10 Hz), 7.44–7.51 (3H, m), 7.67 (1H, d, J = 8.10 Hz), 10.14 (1H, s); IR (neat) 1633, 1696, 1716, 1730 cm^{-1}.

1-[[2-(1,6-Dioxanyl)-6-(benzyloxy)phenyl]hydroxymethyl]-2,6-bis(methoxymethoxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]benzene (35). ^{n}BuLi (18.5 mL of a 2.5 M solution in hexanes, 40.2 mmol) was added dropwise to a solution of **23** (15.8 g, 46.3 mmol) in dry THF at 0 °C over a 5 min period. Stirring was then continued for 60 min whereupon this solution was added *via* cannula to a solution of aldehyde **11** (12.0 g, 40.2 mmol) in anhydrous THF at 0 °C. The light yellow solution was allowed to stir at 0 °C for 2 h and then allowed to warm to ambient temperature and stirring continued overnight. The reaction mixture was quenched with saturated ammonium chloride solution and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, 2:1 hexanes–ethyl acetate) to afford alcohol **35** as a white foam (18.8 g, 73%): ^{1}H NMR ($CDCl_3$) 0.09 (6H, s), 0.93 (9H, s), 1.41 (1H, br d, J = 13.61 Hz), 2.13–2.23 (1H, m), 3.16 (6H, s), 3.91–4.07 (2H, m), 4.17–4.32 (2H, m), 4.68 (2H, s), 4.78 (1H, d, J = 6.54 Hz), 4.86–4.92 (4H, AB quartet, J_{AB} = 6.72 Hz), 4.94 (2H, s), 6.31 (1H, s), 6.71 (1H, d, J = 6.53 Hz), 6.74 (2H, s), 6.80 (1H, d, J = 7.27 Hz), 7.02–7.06 (2H, m), 7.14 (1H, t, J = 8.12 Hz), 7.24–7.27 (3H, m), 7.38 (1H, d, J = 7.69 Hz); IR (KBr) 1588, 3507 cm^{-1}. Anal. Calcd for $C_{35}H_{48}O_9Si$: C, 65.60; H, 7.55. Found: C, 65.20; H, 7.82.

2-(1,6-Dioxanyl)-6′-(benzyloxy)-2,6-bis(methoxymethoxy)-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-benzophenone (36). Alcohol **35** (18.7 g, 29.2 mmol) was dissolved in methylene chloride and MnO_2 (25.4 g, 0.292 mol) added in portions. The reaction mixture was allowed to stir overnight at ambient temperature at which time an additional 10 g of MnO_2 was added and stirring continued for 2 days. The catalyst was removed by filtration through Celite and washed with further methylene chloride. The filtrates were evaporated to provide benzophenone **36** (17.4 g, 93%) as a white foam: ^{1}H NMR ($CDCl_3$) 0.11 (6H, s), 0.96 (9H, s), 1.38 (1H, br d, J = 12.2 Hz), 2.13–2.32 (1H, m), 3.14 (6H, s), 3.82–3.95 (2H, m), 4.18 (2H, dd, J = 5.19, 10.87 Hz), 4.72 (2H, s), 4.81 (4H, s), 4.86 (2H, s), 5.67 (1H, s), 6.72 (2H, s), 6.83 (1H, d, J = 8.25 Hz), 6.92–6.94 (2H, m), 7.22–7.25 (3H, m), 7.30 (1H, d, J = 8.10 Hz), 7.41 (1H, d, J = 7.2 Hz).

3,5-Bis(methoxymethoxy)-4-[2-benzyloxy)-6-(1,6-dioxanyl)benzoyl]benzyl Alcohol (37). Tetrabutylammonium fluoride (34.7 mL of a 1.0 M solution in THF, 34.7 mmol) was added dropwise to a solution of **36** (18.5 g, 29.0 mmol) in anhydrous THF and allowed to stir at ambient temperature for 1.5 h. Brine was added, and the aqueous layer was extracted with ethyl acetate. The combined organics were washed with brine. All the aqueous extracts were combined and back-extracted with methylene chloride. The organic extracts were similarly combined, dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2, 2:1 ethyl acetate–hexanes) to afford the title compound **37** (13.4 g, 88%) as a white solid: mp 130–2 °C; ^{1}H NMR ($CDCl_3$) 1.38 (1H, br d, J = 13.49 Hz), 1.90 (1H, br t, J = 5.51 Hz), 2.15–2.33 (1H, m), 3.14 (6H, s), 3.84–3.96 (2H, m), 4.20 (2H, dd, J = 4.28, 11.30 Hz), 4.65 (1H, d, J = 4.5 Hz), 4.83 (4H, s), 4.85 (2H, s), 5.69 (1H, s), 6.70 (2H, s), 6.84 (1H, d, J = 8.24 Hz), 6.91–6.94 (2H, m), 7.22–7.27 (3H, m), 7.31 (1H, t, J = 8.12 Hz), 7.43 (1H, d, J = 8.00 Hz); ^{13}C NMR ($CDCl_3$) 26.42, 56.42, 65.61, 68.02, 70.94, 94.56, 100.16, 106.67, 113.04, 120.05, 122.10, 128.16, 128.37, 128.83, 131.33, 131.58, 136.85, 139.72, 145.49, 156.31, 156.66, 195.52; IR (KBr) 1591, 1655, 3486 cm^{-1}. Anal. Calcd for $C_{29}H_{32}O_9 \cdot 0.2H_2O$: C, 65.95; H, 6.18. Found: C, 65.73; H, 6.12.

4-[2-(Benzyloxy)-6-(1,6-dioxanyl)benzoyl]-3,5-bis-(methoxymethoxy)benzaldehyde (38). MnO_2 (*ca.* 10 g) was added in portions to a solution of alcohol **37** (13.1 g, 0.025 mol) in methylene chloride and allowed to stir for 2 days at ambient temperature. The catalyst was removed by filtration through Celite, and the filtrates were evaporated to yield the title aldehyde **38** (12.7 g, 97%) as a white solid. An analytical sample could be prepared by crystallization from ethyl acetate: mp 134–6 °C; ^{1}H NMR ($CDCl_3$) 1.42 (1H, br d, J = 13.61 Hz), 2.17–2.36 (1H, m), 3.17 (6H, s), 3.90–3.98 (2H, m), 4.22 (2H, dd, J = 5.00, 10.80 Hz), 4.80 (2H, s), 4.84 (4H, s), 5.75 (1H, s), 6.87–6.90 (3H, m), 7.14 (2H, s), 7.15–7.30 (3H, m), 7.38 (1H, t, J = 8.06 Hz), 7.48 (1H, d, J = 7.82 Hz), 9.89 (1H, s); IR (KBr) 1588, 1693, 1745 cm^{-1}. Anal. Calcd for $C_{29}H_{30}O_9 \cdot 0.1H_2O$: C, 66.43; H, 5.81. Found: C, 66.23; H, 6.18.

4-[2-(Benzyloxy)-6-(1,6-dioxanyl)benzoyl]-3,5-bis-(methoxymethoxy)benzoic Acid (39). A solution of aldehyde **38** (10.06 g, 19.25 mmol) and NaH_2PO_4 (0.81 g, 6.74 mmol) in MeCN–H_2O (6:1 v/v, 120 mL total volume) was cooled in an ice bath. H_2O_2 (2.3 mL of a 30% solution in water) was added followed by solid sodium chlorite (3.4 g of 80% material), and the mixture was stirred for 1 h when the solvents were removed *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer extracted several times with methylene chloride. The organics were combined, dried ($MgSO_4$), and evaporated to give the title compound **39** as a white solid (10.2 g, 98%). An analytical sample could be prepared by recrystallization from EtOAc–hexanes: mp 158–9 °C; ^{1}H NMR ($CDCl_3$) 1.42 (1H, br d, J = 12.60 Hz), 2.18–2.33 (1H, m), 3.16 (6H, s), 3.88–3.99 (2H, m), 4.22 (1H, dd, J = 5.31, 10.99 Hz), 4.82 (2H, s), 4.84 (4H, s), 5.74 (1H, s), 6.89 (3H, m), 7.21–7.40 (6H, m), 7.47 (1H, d, J = 7.14 Hz); ^{13}C NMR ($CDCl_3$) 26.43, 56.54, 68.02, 71.15, 94.45, 99.99, 110.14, 112.90, 120.30, 127.70, 128.57, 128.74, 128.95, 130.21, 131.96, 132.10, 136.24, 140.22, 155.84, 156.83, 171.32, 195.22; IR (KBr) 1589, 1690, 1721 cm^{-1}. Anal. Calcd for $C_{29}H_{30}O_{10}$: C, 64.68; H, 5.61. Found: C, 64.73; H, 5.68.

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