A General, Regioselective Synthesis of Substituted Benzocyclobutenedione Monoacetals

James P. Edwards,[1] Damian J. Krysan, and Lanny S. Liebeskind*

Sanford S. Atwood Chemistry Center, Emory University, 1515 Pierce Drive, Atlanta, Georgia 30322

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A general, regioselective synthesis of substituted benzocyclobutenedione monoacetals is reported. Palladium-catalyzed coupling of a variety of 4-chlorocyclobutenones with 3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 2-(ethylene acetal) and heating up to 70–100 °C produces substituted benzocyclobutenedione monoacetals in good to excellent yields. This chemistry is presumed to proceed through palladium-catalyzed formation of a 3-(1-oxo-2-cyclobuten-4-yl)-3-cyclobutene-1,2-dione-2-(ethylene acetal) followed by a thermally induced ring opening to a dienyl ketene and subsequent six-electron electrocyclic ring closure and tautomerization. 2,3-Disubstituted 4-chlorocyclobutenones afford palladium intermediates which couple exclusively at the least-substituted allylic terminus. 2,3,4-Trisubstituted 4-chlorocyclobutenones have not been studied in detail; however, preliminary results suggest that regioselective allylic cross-coupling can be achieved. The methodology described provides an expedient and efficient route to previously difficult-to-prepare benzocyclobutenedione derivatives. These function as important synthetic intermediates in a variety of reactions developed in these and other laboratories.

Introduction

The synthetic utility of ring-enlargement reactions of small-ring compounds in organic synthesis has been well documented.[2-9] In this regard, ring expanding transformations proceeding from cyclobutenones and cyclobutenediones have proven very useful.[10-13] In particular, the conversion of 4-alkynyl (or 4-alkenyl, -aryl, or -heteroaryl) cyclobutenones into quinones and phenols has been intensively studied by the groups of Danheiser,[14-19] Moore,[20-27] and Liebeskind.[10,28-32] The Danheiser approach relies upon the [2 + 2] cycloaddition of transient vinylketenes to alkynes to obtain the requisite cyclobutenones; whereas the latter research groups have developed protocols for the construction of substituted cyclobutenones via cyclobutenediones (prepared from squaric acid esters) to achieve both similar and complementary substitution patterns. In addition, a variety of functionalized cyclopentenones can be obtained under proper conditions from ring expansion reactions of 4-alkynyl-[13,33,35] and 4-allenylcyclobutenones.[36]

All of the transformations proceeding through cyclobutenediones also are viable using benzocyclobutenediones. Many cyclobutenedione substitution patterns can be constructed in a straightforward manner; however, the same cannot be said of benzocyclobutenediones. This deficiency has not been due to a lack of attention. Since Cava's first report of the parent compound in 1957,[37,38] a

(1) National Institutes of Health Postdoctoral Fellow, 1991-1993.
(2) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH Verlagsgesellschaft: Weinheim, Fed Rep Ger, 1991.
(3) Trost, B. M. *Strain and Reactivity: Partners for Selective Synthesis*; de Meijere, A., Ed.; Topics in Current Chemistry Springer-Verlag: Berlin, 1986; Vol. 133, p 3.
(4) Wong, H. C. N.; Lau, K.-L.; Tam, K.-F. *The Application of Cyclobutane Derivatives in Organic Synthesis*; de Meijere, A., Ed.; Topics in Current Chemistry; Springer-Verlag: Berlin, 1986; Vol. 133, p 83.
(5) Salaün, J. R. Y. *Synthesis and Synthetic Applications of 1-Donor Substituted Cyclopropanes with Ethynyl, Vinyl and Carbonyl Groups*; de Meijere, A., Ed.; Topics in Current Chemistry; Springer Verlag: Berlin, 1988; Vol. 144; pp 1.
(6) Reissig, H. U. *Donor-Acceptor-Substituted Cyclopropanes: Versatile Building Blocks in Organic Synthesis*; de Meijere, A., Ed.; Topics in Current Chemistry; Springer Verlag: Berlin, 1988; Vol. 144, p 73.
(7) Krief, A. *Synthesis and Synthetic Applications of 1-Metallo-1-Selenocyclopropanes and -cyclobutanes and Related 1-Metallo-1-silylcyclopropanes*; de Meijere, A., Ed.; Topics in Current Chemistry; Springer-Verlag: Berlin, 1987; Vol. 135, p 1.
(8) Binger, P.; Büch, H. M. *Cyclopropenes and Methylenecyclopropenes as Multifunctional Reagents in Transition Metal Catalyzed Reactions*; de Meijere, A., Ed.; Topics in Current Chemistry; Springer-Verlag: Berlin, 1987; Vol. 135, p 77.
(9) Baird, M. S. *Functionalized Cyclopropenes as Synthetic Intermediates*; de Meijere, A., Ed.; Topics in Current Chemistry; Springer Verlag: Berlin, 1988; Vol. 144, p 137.
(10) Liebeskind, L. S. *Tetrahedron Symposium in Print* **1989**, *45*, 3053.
(11) Durst, T.; Breau, L. *Cyclobutene Ring Opening Reactions*; Trost, B. M., Fleming, I., Ed.; Comprehensive Organic Synthesis; Pergamon: New York, 1991; Vol. 6, p 675.
(12) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821.
(13) Liebeskind, L. S.; Chidambaram, R.; Mitchell, D.; Foster, B. *Pure Appl. Chem.* **1988**, *60*, 2734.
(14) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149.
(15) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
(16) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.
(17) Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527.
(18) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693.
(19) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917.
(20) Ezcurra, J. E.; Pham, C.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 4787.
(21) Xia, H. J.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 3765.
(22) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 326.
(23) Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 4048.
(24) Xu, S. L.; Taing, M.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6104.
(25) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897.
(26) Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177.
(27) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.
(28) Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.
(29) Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412.
(30) Liebeskind, L. S.; Zhang, J. *J. Org. Chem.* **1991**, *56*, 6379.
(31) Liebeskind, L. S.; Foster, B. F. *J. Am. Chem. Soc.* **1990**, *112*, 8612.
(32) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065.
(33) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.
(34) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291.
(35) Liebeskind, L. S.; Mitchell, D.; Foster, B. *J. Am. Chem. Soc.* **1987**, *109*, 7908.
(36) Stone, G. B.; Liebeskind, L. S. *J. Org. Chem.* **1990**, *55*, 4614.
(37) Cava, M. P.; Napier, D. R. *J. Am. Chem. Soc.* **1957**, *79*, 3606.
(38) Cava, M. P.; Napier, D. R.; Pohl, R. J. *J. Am. Chem. Soc.* **1963**, *85*, 2076.

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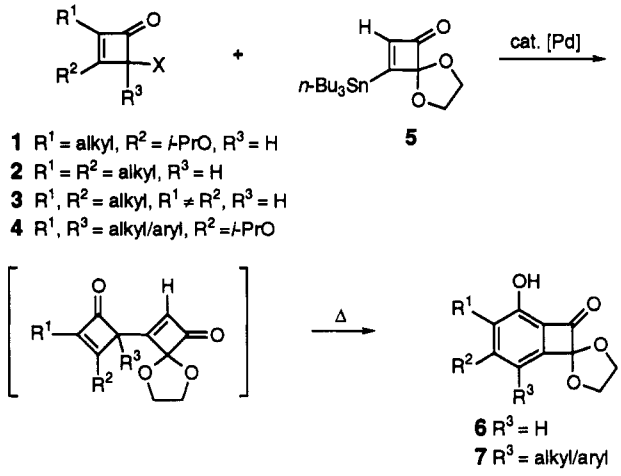
Scheme I

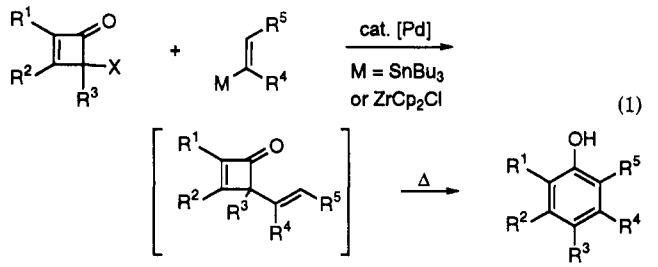


number of papers describing approaches to substituted benzocyclobutenediones have appeared;[39-43] however, the reaction conditions used preclude the construction of many functionalized derivatives. Related benzocyclobutenedione monoacetals have been prepared by Swenton for use as 1,4-dipole equivalents in an annulative approach to anthraquinones.[44-47]

Herein is reported a general, regioselective route to a variety of benzocyclobutenedione monoacetals and the benzocyclobutenediones derived from them. The preparation of these benzocyclobutenedione derivatives promises to greatly expand the utility of synthetic organic methodologies based on their transformations.

Results and Discussion

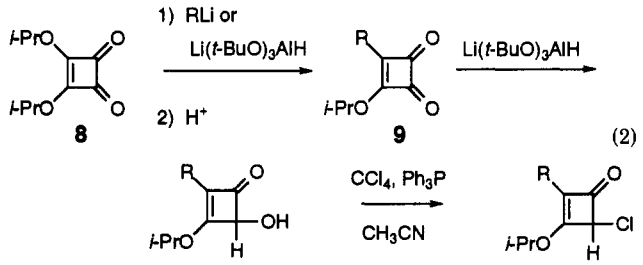
An earlier paper from these laboratories described a versatile synthesis of a variety of phenols from 4-chlorocyclobutenones and aryl- and alkenylstannanes (eq 1).[29]



(1)

The process was designed to provide 4-vinyl-(or aryl- or heteroaryl-)cyclobutenones via a palladium catalyzed cross-coupling process.[48,49] The cross-coupled products, in turn, would be transformed to substituted phenols on thermolysis. It was recognized that a powerful synthesis of substituted benzocyclobutenedione derivatives could be realized using a stannylcyclobutenedione[50] or stannylcyclobutenedione monoacetal[50] as the organostannane coupling partner (Scheme I). The synthesis of the required 4-chlorocyclobutenones 1–4 and the key stannylated cyclobutenedione derivative, 3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 2-(ethylene acetal) (5), and their subsequent conversion to benzocyclobutenedione monoacetals, 6 and 7, are described below.

2-Substituted-3-alkoxy-4-chlorocyclobutenones (1a–e). The synthesis of 4-chlorocyclobutenones bearing an alkyl or phenyl substituent at C(2) and an alkoxy substituent at C(3) follows the route described earlier[29] and is outlined in eq 2. Treatment of diisopropyl squarate (8)

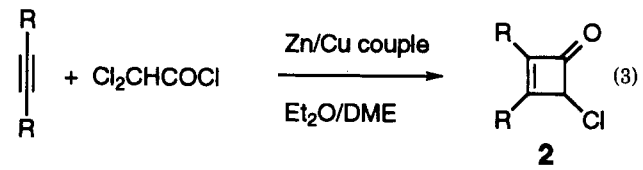


(2)

a, R = CH_3; b, R = *n*-Bu; c, R = *s*-Bu; d, R = *t*-Bu; e, R = Ph

with an organolithium reagent followed by acid-catalyzed elimination of *i*-PrOH provided the cyclobutenediones **9a–e** in excellent yields (90–99%). Monoreduction of diones **9a–e** with Li(*t*-BuO)$_3$AlH was highly selective for the non-vinylogous ester carbonyl, affording 4-hydroxycyclobutenones **10a–d** in 85–95% yields and **10e** in 68% yield. Conversion of **10a–e** to the chlorides **1a–e** with Ph_3P/CCl_4 proceeded in good yields (85–95%). The C(2)-unsubstituted derivative, 4-chloro-3-isopropoxycyclobutenone (**1**, R = H) could not be obtained by this method; reduction of 3-isopropoxy-3-cyclobutene-1,2-dione with Li(*t*-BuO)$_3$AlH proceeded cleanly at −78 °C, but the resulting alcohol was not isolable, undergoing decomposition at ambient temperatures.

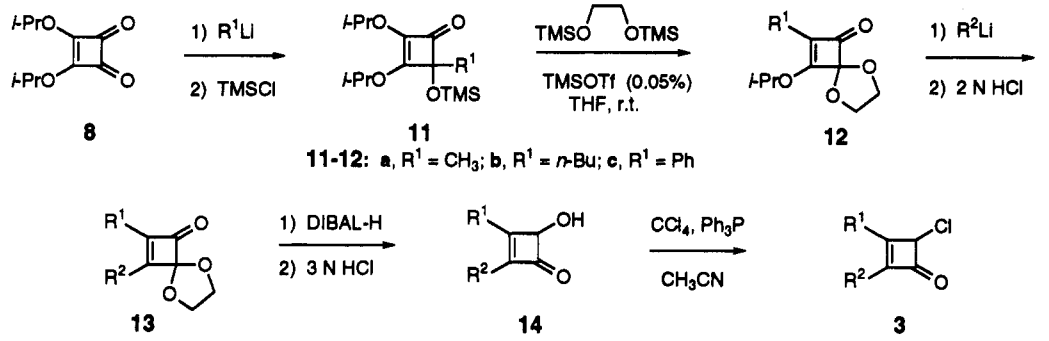
2,3-Dialkyl-4-chlorocyclobutenones, R^1 = R^2 (2). The synthesis of 4-chlorocyclobutenones bearing the same alkyl substituent at both C(2) and C(3) was most easily achieved utilizing a [2 + 2] cycloaddition of monochloroketene with a symmetrically substituted acetylene (eq 3). For example, generation of monochloroketene, following a modification of the procedure reported by Danheiser for the generation of dichloroketene,[51] in the presence of 3-hexyne afforded 4-chloro-2,3-diethylcyclobutenone (**2**, R = Et), in 35–40% isolated yield. Although the yield of this reaction is only moderate, the required chloride is obtained in a single step.



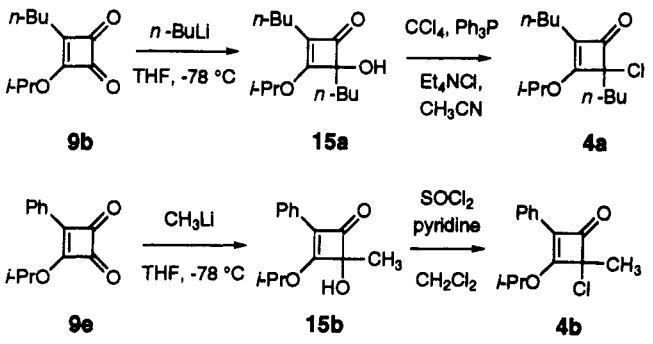
(3)

(39) South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815.
(40) Liebeskind, L. S.; Lescosky, L. J.; McSwain, C. M., Jr. *J. Org. Chem.* **1989**, *54*, 1435.
(41) Bradley, J. C.; Durst, T. *J. Org. Chem.* **1991**, *56*, 5459.
(42) Aidhen, I.; Narasimhan, N. *Tetrahedron Lett.* **1991**, *32*, 2171.
(43) Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.
(44) Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989.
(45) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825.
(46) Anderson, D. K.; Coburn, C. E.; Haag, A. P.; Swenton, J. S. *Tetrahedron Lett.* **1983**, *24*, 1329.
(47) Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1800.
(48) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
(49) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
(50) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.
(51) Danheiser, R. L.; Savariar, S.; Cha, D. D. *3-Butylcyclobutenone-(2-Cyclobuten-1-One, 3-Butyl)*; White, J. D., Boeckman, R. K., Coffen, D. L., Meyers, A. I., Overman, L. E., Paquette, L. A., Smart, B. E., Winterfeldt, E., Yamamoto, H., Eds.; Organic Syntheses John Wiley & Sons Inc: New York, 1990; Vol. 68, pp 32.

Scheme II



Scheme III

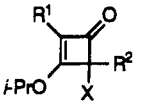


2,3-Disubstituted-4-chlorocyclobutenones, $R^1 \neq R^2$ (3a–d). As previously demonstrated, the regiocontrol obtained in the synthesis of cyclobutenedione monoacetals can be exploited in the synthesis of 4-chlorocyclobutenones bearing different substituents at C(2) and C(3) (Scheme II).[29] Treatment of diisopropyl squarate with an organolithium reagent, followed by in-situ trapping of the alkoxide with TMSCl afforded excellent yields of the silyl ethers **11a–c**.[52] Acetalization under Noyori's conditions,[53] afforded the acetals **12a–c**.[54] Addition of a second organolithium reagent, followed by mild acid hydrolysis, provided access to the regioisomeric cyclobutenedione monoacetals **13a–d**. Reduction of the carbonyl with diisobutylaluminum hydride and subsequent acetal deprotection afforded the 4-hydroxycyclobutenones **14a–d**. Conversion of the alcohols **14** to the chlorides **3a–d** with Ph_3P/CCl_4 was facile.

2,4-Disubstituted-3-alkoxy-4-chlorocyclobutenones. The preparation of fully substituted benzocyclobutenediones requires the use of 2,3,4-trisubstituted 4-chlorocyclobutenones. In the current study two examples were prepared, one bearing the same substituent at C(2) and C(4) (**4a**) and the other bearing different substituents to test the potential for regiocontrol in the Stille cross-coupling step (**4b**) (Scheme III). Addition of *n*-BuLi to cyclobutenedione **9b** afforded the tertiary alcohol **15a** in 75% yield. Chlorination of **15a** under the conditions described above for alcohols **10** and **14** provided variable (20–50%) yields of **4a**; however, the presence of 10–15% Et_4NCl led to cleaner reactions and **4a** was obtained reproducibly in 74–76% yield.

Likewise, treatment of **9e** with CH_3Li afforded **15b** in 89% yield. Unfortunately, the chlorination conditions optimized for **4a** required a chromatographic purification of the product, and **4b** proved to be only moderately stable to silica gel. This resulted in unacceptable yields of product (25–40%). On the other hand, treatment of **15b** with $SOCl_2$/pyridine following the procedure of Moore and Xu[22] gave crude product that was efficiently purified by recrystallization. On the basis of the results of Moore and Xu, the product was expected to be the 2-methyl-4-phenyl isomer, i.e., chlorination next to the phenyl group. However, examination of the ^{13}C NMR of the product showed it to be the 4-methyl-2-phenyl isomer **4b** (Scheme III). In ^{13}C NMR spectra of 2-methyl-3-isopropoxycyclobutenones, the methyl groups at C(2) are observed upfield of 10 ppm (Table I). The chloride obtained from treatment of **15b** with $SOCl_2$/pyridine showed a methyl group resonance at 22.9 ppm indicating assignment as the 4-methyl regioisomer **4b** in consonance with the data obtained for alcohol **15b** (Table I, entry 3, CH_3 resonance at 20.6 ppm). The ^{13}C NMR data for the known regioisomeric 4-hydroxy-2-methyl-3-isopropoxy-4-phenyl-2-cyclobutenone (**15c**)[28] (CH_3 resonance at 6.52 ppm) further supported the structural assignment of **4b** (Table I, entry 4).

Table I. ^{13}C NMR Chemical Shifts of C(2) and C(4) Methyls in 3-Isopropoxycyclobutenones



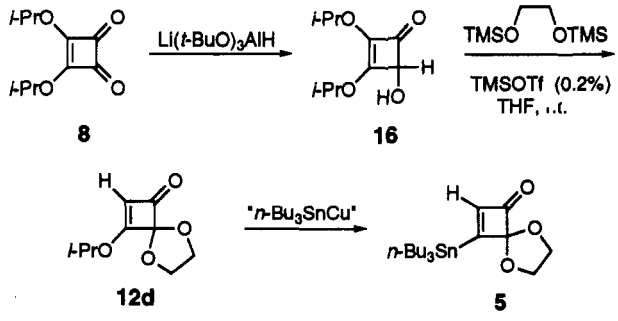
				^{13}C shift (ppm)		
entry	R^1	R^2	X	C(2) CH_3	C(4) CH_3	ref
1	CH_3	H	OH	5.90	–	*a*
2	CH_3	CH_3	OH	6.58	19.20	*b*
3	Ph	CH_3	OH	–	20.60	*b*
4	CH_3	Ph	OH	6.52	–	*c*
5	CH_3	H	Cl	6.90	–	*a*
6	CH_3	CH_3	Cl	6.98	22.04	*b*
7	Ph	CH_3	Cl	–	22.92	*b*

[a] Krysan, D. J.; Gurski, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 1412. [b] This work. [c] Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.

3-(Tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 2-(Ethylene acetal) (5). The preparation of stannylcyclobutenone **5** was accomplished in three steps from diisopropyl squarate (Scheme IV). The acetal **12d** was prepared in a manner similar to that described above for **12a–c**; however, in this case the alcohol **16**, obtained by Li(*t*-BuO)$_3$AlH reduction of diisopropyl squarate, need not be silylated prior to the Noyori acetalization. Although **5** could be prepared in moderate yields from **12d** by

(52) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *33*, 2482.
(53) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 1357.
(54) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350.

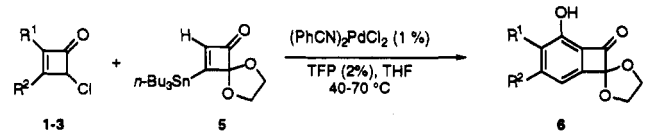
Scheme IV



cyanide-catalyzed addition of $(CH_3)_3SiSnBu_3$,[55] a more efficient and cleaner route was developed. Using a modification of Lipshutz' method of stannyl cuprate formation from $(n\text{-Bu})_2Cu(CN)Li$ and $(CH_3)_3SiSnBu_3$,[56,57] stannane **5** could be obtained in 70–80% yield from **12d**. The primary modification to the experimental protocol is a considerably lengthened time of mixing of $(CH_3)_3SiSnBu_3$ and $(n\text{-Bu})_2Cu(CN)Li$ at room temperature prior to addition of **12d** at −78 °C (see Experimental Section). This affords a black heterogeneous reaction mixture, the composition of which has yet to be determined. Other methods of stannyl cuprate formation[58–61] afforded variable, low yields of **5** from **12d**.

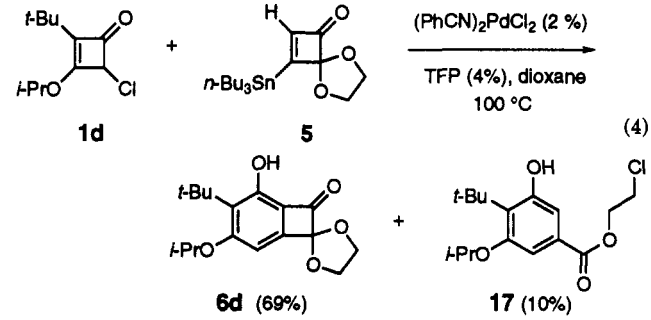
Preparation of Trisubstituted Benzocyclobutenedione Monoacetals 6. With the requisite 4-chlorocyclobutenones **1–3** and stannylcyclobutenone **5** in hand, the Stille cross-coupling/rearrangement sequence was examined. In recent years, a great deal of attention has been given to ligand effects in palladium-catalyzed reactions,[62–65] and recent work by Farina[66–70] has shown that weaker donor ligands such as tris(2-furyl)phosphine (TFP) and triphenylarsine[71] provide access to more reactive Stille cross-coupling catalysts than the classic triphenylphosphine-based systems. In earlier work concerning the coupling of 4-chlorocyclobutenones with various organostannanes, the $(PhCN)_2PdCl_2$/TFP system was found to be optimal.[29] Typical catalyst loadings were 5% Pd and 10% TFP (2:1 ligand/Pd ratio). This same catalyst system worked well in the coupling of 4-chlorocyclobutenones **1–3** with **5** as well, with the exception that lower catalyst loadings (0.4–1 mol%) were required. The

Table II. Synthesis of Benzocyclobutenones



entry	R^1	R^2	product	yield, %
1	CH_3	*i*-PrO	**6a**	95
2	*n*-Bu	*i*-PrO	**6b**	99
3	*s*-Bu	*i*-PrO	**6c**	91
4	*t*-Bu	*i*-PrO	**6d**	69
5	Ph	*i*-PrO	**6e**	90
6	Et	Et	**6f**	61
7	CH_3	Ph	**6g**	56
8	Ph	CH_3	**6h**	75
9	CH_3	*n*-Bu	**6i**	72
10	*n*-Bu	CH_3	**6j**	71

results are collected in Table II. For example, treatment of **1a** with a 5% excess of **5** in THF (0.4 M) with 1 mol% $(PhCN)_2PdCl_2$ and 2 mol% TFP followed by heating to 60–65 °C provided benzocyclobutenone **6a** in 91–95% isolated yields (Table II, entry 1). It is interesting to note that **1a** reacts more slowly with other aryl- and alkenylstannanes than it does with **5**; the coupling/rearrangement of **1a** with trimethylstannylbenzene requires temperatures of 90–100 °C for efficient rearrangement to the phenol.[29] The remaining 4-chlorocyclobutenones **1–3** also reacted with **5** to afford good to excellent yields of benzocyclobutenones **6** (Table II). Typically, these reactions required 2–4 h at 50–65 °C to go to completion, with the exception of the highly hindered cyclobutenone **1d** bearing a *tert*-butyl at C(2) (entry 4). Using 2 mol% Pd, this substrate required 16–18 h at 65 °C to be consumed, but still provided **6d** in 69% yield. Changing the solvent to dioxane and increasing the reaction temperature to 100 °C reduced the reaction time to 3 h, again providing **6d** in 68%; however, a byproduct identified as 2-chloroethyl (4-*tert*-butyl-5-hydroxy-3-isopropoxy)benzoate (**17**) was also isolated from this reaction in 10% yield (eq 4). An

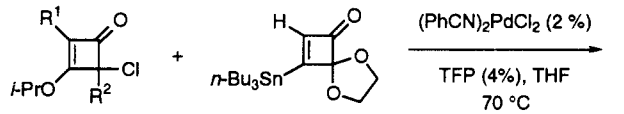


(4)

analogous ring-opened byproduct was observed in reactions of **3c** with **5** that were heated above 60 °C, and the susceptibility of benzocyclobutenedione **6g** to suffer ring-cleavage under the palladium-catalyzed coupling conditions may account for the low yield in entry 7. As can be seen in Table II, 4-chlorocyclobutenones bearing an isopropoxy group at C(3) generally provided higher yields of **6** (entries 1–5).

Gratifying, the fully substituted 4-chlorocyclobutenones **4a** and **4b** also participated well in the benzannulation reaction. These substrates, like the disubstituted 4-chlorocyclobutenone, **1d**, required 2 mol% Pd and 16–24 h at 65 °C for complete consumption of starting material and afforded benzocyclobutenones **7a** and **7b**/**7c** in 79% and 57% yield, respectively (eq 5). The product obtained from

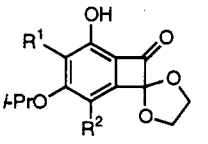
(55) Chenard, B.; Langanis, E.; Davidson, F.; Rajanbabu, T. *J. Org. Chem.* **1985**, *50*, 3666.
(56) Lipshutz, B. H.; Reuter, D. C.; Ellsworth, E. L. *J. Org. Chem.* **1989**, *54*, 4975.
(57) Lipshutz, B. H.; Sharma, S.; Reuter, D. C. *Tetrahedron Lett.* **1990**, *31*, 7253.
(58) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905.
(59) Piers, E.; Tillyer, R. D. *J. Org. Chem.* **1988**, *53*, 5366.
(60) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065.
(61) Oehlschlager, A. C.; Hutzinger, M. W.; Aksela, R. *Tetrahedron Lett.* **1990**, *31*, 165.
(62) Saa, J. M.; Martorelli, G.; Garciaraso, A. *J. Org. Chem.* **1992**, *57*, 678.
(63) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995.
(64) van Asselt, R.; Elsevier, C. J. *Organometallics* **1992**, *11*, 1999.
(65) Trost, B.; Edstrom, E.; Carter-Petillo, M. *J. Org. Chem.* **1989**, *54*, 4489.
(66) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243.
(67) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *13*, 9585.
(68) Farina, V.; Hauck, S. I. *Synlett* **1991**, 157.
(69) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833.
(70) Farina, V.; Baker, S. R.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 6043.
(71) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1981**, *205*, C27.



4a $R^1 = R^2 = n$-Bu
4b R^1 = Ph, $R^2 = CH_3$

5

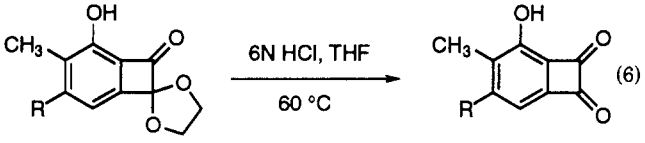
(5)



7a $R^1 = R^2 = n$-Bu
7b $R^1 = CH_3$, R^2 = Ph
7c R^1 = Ph, $R^2 = CH_3$

coupling of **4b** afforded a 2:1 ratio of regioisomers, the major isomer **7b** resulting from coupling at the phenyl-bearing carbon of the π-allyl palladium intermediate. The assignment of structures **7b** and **7c** was based upon ^{13}C NMR chemical shift data. The ^{13}C NMR shift of the C(4) methyl of **7b** was observed 1.89 ppm upfield of the C(6) methyl of **7c** and this is consistent with other phenol regioisomer assignments made previously.[72] In addition, the two protons of the dioxolane ring *syn* to the C(6) phenyl in **7b** are significantly (0.27 ppm) shielded by the phenyl ring in the ^1H NMR of this molecule. The selective formation of isomer **7b**, though of modest proportions, is deemed significant. It is anticipated that greater selectivities can be achieved through screening of ligand effects and other reaction parameters. These studies, within the full context of the benzannulation method, will be the subject of future investigation.

The benzocyclobutenedione monoacetals **6** and **7** are easily transformed to the parent benzocyclobutenediones **18** by treatment with 6 N HCl in refluxing THF. For example, **6a** and **6i** were deprotected in 99 and 98% yield, respectively (eq 6).



(6)

6a: R = *i*-PrO
6i: R = *n*-Bu

18a: R = *i*-PrO
18i: R = *n*-Bu

Conclusion

The results described above demonstrate that the palladium-catalyzed coupling of 4-chlorocyclobutenones **1–4** with stannylcyclobutenone **5** followed by thermolysis provide benzocyclobutenedione monoacetal derivatives of varying substitution patterns. These compounds have been demonstrated to be valuable precursors to anthraquinones,[44–47] and the parent benzocyclobutenediones are useful in many ring-enlargement reactions.[11,13,34,35,73,74] Further studies on the use of benzocyclobutenedione acetals **6** and **7** in substituted anthraquinone syntheses, as well as efforts to control the regioselectivity in couplings of 2,4-dialkyl-4-chlorocyclobutenones, will be reported in due course.

Experimental Section

General Experimental. ^1H and ^{13}C NMR spectra were recorded on a General Electric QE-300 (300 MHz ^1H, 75.5 MHz ^{13}C) spectrometer in deuteriochloroform ($CDCl_3$) with either tetramethylsilane (TMS) (0.00 ppm ^1H, 0.00 ppm ^{13}C) or chloroform (7.26 ppm ^1H, 77.00 ppm ^{13}C) as an internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), hex (hextet), hept (heptet), m (multiplet), exch (exchangeable), app (apparent)); coupling constants, J, are reported (Hz); integration is provided; and assignment is indicated. Infrared spectra were recorded on a Nicolet 510 FT-IR spectrometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67–100%), m (medium 40–67%), w (weak 20–40%), and br (broad). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light, iodine, or *p*-anisaldehyde solution. Solvents for extraction and chromatography were reagent grade and used as received. Flash column chromatography was performed by the method of Still with 32–63 μm silica gel (Woelm). Solvents used as reaction media were distilled immediately before use: Et_2O, THF, and toluene were distilled from Na/benzophenone ketyl; CH_2Cl_2, 1,2-dichloroethane (DCE), and CH_3CN were distilled from CaH_2. Bulb-to-bulb ("Kugelrohr") distillations were done on a Buchi GKR-50 Kugelrohr, and boiling points (bp) correspond to uncorrected air bath temperatures.

All reactions were performed under a dry argon atmosphere in oven- and/or flame-dried glassware, except for those reactions utilizing water as a solvent, which were run under air. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl, $NaHCO_3$, KOH, NaOH, KF, sodium potassium tartrate, and $Na_2S_2O_3$ refer to aqueous solutions.

The following compounds were prepared by literature methods: diisopropyl squarate (**8**),[52] 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione (**9a**),[52] 3-isopropoxy-4-*n*-butyl-3-cyclobutene-1,2-dione (**9b**),[52] 3-isopropoxy-4-*tert*-butyl-3-cyclobutene-1,2-dione (**9d**),[52] 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (**9e**),[52] 3-isopropoxy-4-hydroxy-2-methyl-2-cyclobuten-1-one (**10a**),[29] 4-chloro-3-isopropoxy-2-methyl-2-cyclobuten-1-one (**1a**),[29] 3-isopropoxy-3-cyclobutenedione 2-(ethylene acetal) (**12d**),[54] 3-isopropoxy-4-methyl-3-cyclobutenedione 2-(ethylene acetal) (**12a**),[54] 4-*n*-butyl-3-isopropoxy-3-cyclobutenedione 2-(ethylene acetal) (**12b**),[54] 3-isopropoxy-4-phenyl-3-cyclobutenedione 2-(ethylene acetal) (**12c**),[54] 3-*n*-butyl-4-methyl-3-cyclobutene-1,2-dione 2-(ethylene acetal) (**13a**),[54] 4-*n*-butyl-3-methyl-3-cyclobutene-1,2-dione 2-(ethylene acetal) (**13b**),[54] 3-methyl-4-phenyl-3-cyclobutenedione 2-(ethylene acetal) (**13c**),[29] 4-methyl-3-phenyl-3-cyclobutenedione 2-(ethylene acetal) (**13d**),[54] 4-hydroxy-3-methyl-2-phenyl-2-cyclobuten-1-one (**14d**),[29] 4-hydroxy-2-methyl-3-phenyl-2-cyclobuten-1-one (**14c**),[29] 4-chloro-3-methyl-2-phenyl-2-cyclobuten-1-one (**3d**),[29] 4-chloro-2-methyl-3-phenyl-2-cyclobuten-1-one (**3c**),[29] tris-(2-furyl)phosphine,[75] bis(benzonitrile)palladium dichloride.[76]

4-Chloro-2,3-diethyl-2-cyclobutenone (2). To a 500-mL round-bottomed flask equipped with a magnetic stirring bar, a dry ice condensor, and a nitrogen inlet was added freshly prepared zinc/copper couple (15.0 g, 0.23 mol, 3.5 equiv) and 250 mL of dry ether. The mixture was cooled to 0 °C and 3-hexyne (5.75 g, 0.07 mol, 1.0 equiv) was added via syringe. The dry ice condensor was filled and the ice bath was removed from the reaction flask. Dichloroacetyl chloride (19.7 g, 0.14 mol, 2.0 equiv), in 40 mL of ether was added dropwise over 1 h while maintaining a gentle reflux. Warming with a heat gun was required to initiate the reaction. After completion of the addition, the solution was stirred for one additional hour. The mixture was poured into

(72) Huffman, M. A.; Liebeskind, L. S.; Pennington, W. T. *Organometallics* **1992**, *11*, 255.
(73) Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 989.
(74) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174.
(75) Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 63.
(76) Doyle, J. R.; Slade, P. E.; Jonassen, H. B. *Inorg. Synth.* **1960**, *6*, 216.

250 mL of ice water. The organic layer was separated and washed with 2 × 150 mL of water and then 2 × 100 mL of saturated $NaHCO_3$, and the ether layer was dried with $MgSO_4$ and concentrated to an orange oil. The resulting crude oil was purified by flash silica gel chromatography (1:4 EtOAc/hexanes, R_f = 0.52) to give 8.35 g (75%) of a clear oil: IR (CH_2Cl_2, cm^{-1}) 2950, 2780, 1770, 1625, 1465; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20 (s, 1H), 2.62 (m, 2H), 2.20 (quartet, J = 7.6 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H), 1.12 (t, J = 7.5 Hz, 3H). Anal. Calcd for $C_8H_{11}OCl$: C, 60.57; H, 6.99. Found: C, 60.29; H, 7.23.

4-*s*-Butyl-3-isopropoxy-3-cyclobutene-1,2-dione (9c). In a 100-mL two-necked flask, a solution of diisopropyl squarate (8) (3.545 g, 17.88 mmol) in 1:1 Et_2O/THF (50 mL) was cooled to −78 °C (CO_2/IPA). To this solution was added *s*-BuLi (1.26 M in cyclohexane; 14.2 mL, 17.9 mmol, 1.0 equiv) dropwise via an addition funnel over a 30-min period. The reaction mixture was stirred 2 h at −78 °C. The reaction mixture was quenched by the slow addition of 1/1 THF/H_2O (30 mL), allowed to warm to room temperature, poured into brine (50 mL), and extracted with EtOAc (3 × 100 mL). The extracts were combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to a yellow oil. The crude product was dissolved in CH_2Cl_2 (100 mL) and treated with concentrated HCl (8 drops). The reaction mixture was stirred at room temperature for 90 min. Solid K_2CO_3 (~1 g) was added and the reaction mixture was stirred vigorously for 15 min. The resulting suspension was filtered through a pad of Celite and concentrated to a yellow oil. Purification by silica gel chromatography (hexane/EtOAc, 12/1) and bulb-to-bulb distillation (120–125 °C/0.5 Torr) afforded 2.434 g (70%) of dione **9c** as a pale yellow liquid. Data for **9c**: bp 120–125 °C (0.5 Torr); ^1H NMR (300 MHz, $CDCl_3$) 5.30 (hept, J = 6.2, 1H, OC*H*), 2.71 (hex, J = 7.0, 1H, C(4)CH), 1.61 (m, 1H, C(4)CHC*H*$_a$H$_b$), 1.50 (m, 1H, C(4)CHCH$_a$*H*$_b$), 1.34 (d, J = 6.2, 6H, OCH(C*H*$_3$)$_2$), 1.14 (d, J = 7.0, 3H, C(4)CHC*H*$_3$), 0.80 (t, J = 7.4, 3H, CH(CH$_3$)CH$_2$C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 197.38, 194.80, 194.21, 188.20, 78.68, 33.33, 26.54, 22.46, 16.23, 11.53; IR (CCl_4, cm^{-1}) 2971 (m), 1794 (s), 1754 (s), 1594 (s), 1391 (s), 1379 (m), 1343 (m), 1320 (m), 1098 (m); TLC R_f 0.43 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{11}H_{16}O_3$ (MW 196.25): C, 67.32; H, 8.22. Found: C, 67.39; H, 8.29.

General Procedure for the Preparation of 3-Alkoxy-2-alkyl-4-hydroxy-2-cyclobuten-1-ones (10b–e): 2-*n*-Butyl-4-hydroxy-3-isopropoxy-2-cyclobuten-1-one (10b). The preparation of 2-*n*-butyl-4-hydroxy-3-isopropoxy-2-cyclobuten-1-one (**10b**) will serve to illustrate the general method of preparation of **10b–e**.

In a 50-mL two-necked flask, a solution of **9b** (1.880 g, 9.58 mmol) in THF (25 mL) was cooled to −42 °C (CO_2/CH_3CN). To this solution was added lithium tri-(*tert*-butoxy)aluminum hydride (1.0 M in THF; 10.1 mL, 10 mmol, 1.1 equiv) slowly via syringe. After 1 h at −42 °C, TLC analysis indicated complete consumption of starting material. The reaction was quenched by the addition of 1/1 THF/H_2O (10 mL). The reaction mixture was allowed to warm to room temperature and poured into 1 N HCl (50 mL). The product was extracted with EtOAc (3 × 75 mL). The extracts were washed with brine (1 × 30 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc, 1/1) and bulb-to-bulb distillation (150–155 °C/0.40 Torr) to afford 1.530 g (81%) of the alcohol **10b** as a clear oil. Data for **10b**: bp 150–155 °C (0.40 Torr); ^1H NMR (300 MHz, $CDCl_3$) 5.38 (br exch, 1H, O*H*), 5.18 (s, 1H, C(4)H), 4.91 (hept, J = 6.2, 1H, C*H*(CH$_3$)$_2$), 2.00 (t, J = 7.2, 2H, C(2)C*H*$_2$), 1.43 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.41 (d, J = 6.2, 3H, CH(C*H*$_3$)CH$_3$), 1.37 (d, J = 6.2, 3H, CH(CH$_3$)C*H*$_3$), 1.29 (m, 2H, C*H*$_2$CH$_3$), 0.86 (t, J = 7.2, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$); 192.06, 181.85, 127.19, 81.35, 77.35, 28.86, 23.15, 22.46, 22.46, 21.42, 13.63; IR (CCl_4, cm^{-1}) 3298 (m), 2985 (m), 2961 (m), 1750 (s), 1617 (s), 1387 (s), 1341 (s), 1322 (s), 1104 (s); TLC R_f 0.14 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{11}H_{18}O_3$ (MW 198.26): C, 66.64; H, 9.15. Found: C, 66.49; H, 9.16.

2-*s*-Butyl-4-hydroxy-3-isopropoxy-2-cyclobuten-1-one (10c). Following the general procedure described above, from **9c** (493 mg, 2.51 mmol) and lithium tri-(*tert*-butoxy)aluminum hydride (1.0 M in THF; 2.52 mL, 2.5 mmol, 1.0 equiv) was obtained 0.52 g of the crude product as a yellow oil. Purification by silica gel chromatography (hexane/EtOAc, 2/1) and bulb-to-bulb distillation (140–145 °C/0.35 Torr) afforded 440 mg (88%) of **10c** as a colorless oil. Data for **10c**: bp 140–145 °C (0.35 Torr); ^1H NMR (300 MHz, $CDCl_3$) 5.48 (br exch, 1H, O*H*), 5.20 (s, 1H, C(4)H), 4.93 (hept, J = 6.2, 1H, OC*H*(CH$_3$)$_2$), 2.22 (hex, J = 7.0, 1H, C(2)C*H*), 1.55 (m, 1H, CH(CH$_3$)C*H*$_a$H$_b$CH$_3$), 1.40 (m, 1H, CH(CH$_3$)CH$_a$*H*$_b$CH$_3$), 1.41 (d, J = 6.2, 3H, OCH(C*H*$_3$)CH$_3$), 1.37 (d, J = 6.2, 3H, OCH(CH$_3$)C*H*$_3$), 1.09 (m, 3H, C(2)CHC*H*$_3$), 0.85 (m, 3H, CH$_2$C*H*$_3$) (The product is obtained as an approximate 1/1 mixture of diastereomers, manifested as a complex pattern for several of the multiplets); ^{13}C NMR (75.5 MHz, $CDCl_3$) 191.74, 181.48, 131.46, 81.22, 77.41, 30.40, 27.48, 23.28, 22.47, 11.79; IR (CCl_4, cm^{-1}) 3288 (br, m), 2967 (m), 1746 (m), 1615 (s), 1463 (m), 1387 (m), 1339 (m), 1318 (m), 1104 (m); TLC R_f 0.09 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{11}H_{18}O_3$ (MW 198.26): C, 66.64; H, 9.15. Found: C, 66.39; H, 9.19.

2-*tert*-Butyl-4-hydroxy-3-isopropoxy-2-cyclobutenone (10d). Following the general procedure described above, from **9d** (1.034 g, 5.27 mmol) and lithium tri-(*tert*-butoxy)aluminum hydride (1.0 M in THF; 5.8 mL, 5.8 mmol, 1.1 equiv) was obtained 1.0 g of the crude product as a white solid. Recrystallization (hexane) afforded 755 mg (72%) of **10d** as white needles. Concentration of the mother liquors and recrystallization (hexane) of the residue afforded an additional 222 mg (21%; 93% total) of **10d** as white needles. Data for **10d**: mp 116–117 °C (hexane); ^1H NMR (300 MHz, $CDCl_3$) 5.17 (br s, 1H, C(4)H), 5.02 (exch, 1H, OH), 4.93 (hept, J = 6.2, 1H, C*H*(CH$_3$)$_2$), 1.42 (d, J = 6.2, 3H, CH(C*H*$_3$)CH$_3$), 1.38 (d, J = 6.2, 3H, CH(CH$_3$)C*H*$_3$), 1.16 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 180.03, 159.59, 135.18, 81.26, 77.20, 30.90, 28.06, 23.44, 22.55; IR (CCl_4, cm^{-1}) 3282 (br, m), 2969 (m), 1744 (s), 1609 (s), 1478 (m), 1399 (m), 1375 (m), 1339 (s), 1102 (s); TLC R_f 0.13 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{11}H_{18}O_3$ (MW 198.26): C, 66.64; H, 9.15. Found: C, 66.53; H, 9.12.

4-Hydroxy-3-isopropoxy-2-phenyl-2-cyclobuten-1-one (10e). Following the general procedure described above, from **9e** (2.246 g, 10.4 mmol) and lithium tri-(*tert*-butoxy)aluminum hydride (1.0 M in THF; 10.5 mL, 10.5 mmol, 1.1 equiv) was obtained 2.3 g of the crude product as a yellow solid. Purification by silica gel chromatography (hexane/EtOAc, 3/1) and recrystallization (Et_2O/hexane) afforded 1.54 g (68%) **10c** as colorless granular crystals. Data for **10c**: mp 110.5–111.0 °C (Et_2O/hexane); ^1H NMR (300 MHz, $CDCl_3$) 7.73 (d, J = 7.1, 2H, *o*-Ph), 7.35 (t, J = 7.1, 2H, *m*-Ph), 7.26 (d, J = 7.0, 1H, *p*-Ph), 5.45 (d, J = 6.2, 1H, C(4)H), 5.14 (hept, J = 6.2, 1H, C*H*(CH$_3$)$_2$), 5.03 (exch d, J = 6.2, 1H, O*H*), 1.55 (d, J = 6.2, 3H, CH(C*H*$_3$)CH$_3$), 1.50 (d, J = 6.2, 3H, CH(CH$_3$)C*H*$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 188.78, 179.69, 128.42, 127.99, 126.82, 82.40, 79.05, 23.53, 22.69; IR (CCl_4, cm^{-1}) 3568 (br w), 1744 (m), 1737 (m), 1630 (s), 1598 (m), 1403 (m), 1389 (m), 1104 (m); TLC R_f 0.16 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{13}H_{14}O_3$ (MW 218.24): C, 71.54; H, 6.47. Found: C, 71.44; H, 6.47.

General Procedure for the Preparation of 4-Chlorocyclobutenones 1b–e and 3a,b: 2-*n*-Butyl-4-chloro-3-isopropoxy-2-cyclobutenone (1b). The preparation of 2-*n*-butyl-4-chloro-3-isopropoxycyclobutenone (**1b**) will serve to illustrate the general method of preparation of **1b–e** and **3a,b**.

In a 25-mL two-necked-flask, Ph_3P (1.22 g, 4.65 mmol, 1.3 equiv) was added to a solution of **10b** (710 mg, 3.58 mmol) in CH_3CN (15 mL). The flask was placed in a bath containing cool (~10 °C) H_2O. To this solution was added CCl_4 (1.73 mL, 17.9 mmol, 5.0 equiv) via syringe. The reaction flask was removed from the cooling bath and allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 1 h and CH_3OH (5 mL) was added. The reaction mixture was stirred at room temperature for an additional 15 min and concentrated, and the residue was dissolved in a minimum of CH_2Cl_2 (~2 mL). The resulting solution was applied to a pad (30 × 40 mm) of silica gel, and the pad was rinsed with 4/1 hexane/EtOAc. The filtrate was concentrated to a clear oil. Purification by silica gel chromatography (hexane/EtOAc, 8/1) and bulb-to-bulb distillation (125–130 °C/0.36 Torr) afforded 729 mg (94%) of the chloride **1b** as a colorless oil. Data for **1b**: bp 125–130 °C (0.36 Torr); ^1H NMR (300 MHz, $CDCl_3$) 5.16 (t, J = 1.2, 1H, C(4)H), 4.83 (hept, J = 6.2, 1H, C*H*(CH$_3$)$_2$), 2.06 (m, 2H, C(2)C*H*$_2$), 1.49 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.45 (d, J = 6.2, 3H, CH(C*H*$_3$)CH$_3$), 1.42

(d, J = 6.2, 3H, $CH(CH_3)CH_3$), 1.30 (m, 2H, CH_2CH_3), 0.88 (t, J = 7.3, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 180.96, 174.76, 127.72, 77.82, 65.91, 28.91, 22.86, 22.47, 22.31, 13.61; IR (CCl_4, cm^{-1}) 2961 (m), 2937 (m), 1777 (s), 1632 (s), 1389 (s), 1378 (m), 1343 (m), 1322 (m), 1100 (m); TLC R_f 0.42 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{11}H_{17}ClO_2$ (MW 216.71): C, 60.97; H, 7.91; Cl, 16.36. Found: C, 61.05; H, 7.95; Cl, 16.29.

2-*s*-Butyl-4-chloro-3-isopropoxy-2-cyclobutenone (1c). Following the general procedure described above, from **10c** (295 mg, 1.49 mmol), Ph_3P (0.53 g, 2.0 mmol, 1.4 equiv), and CCl_4 (0.72 mL, 7.5 mmol, 5.0 equiv) in CH_3CN (8 mL) was obtained 0.35 g of crude product. Purification by silica gel chromatography (hexane/EtOAc, 12/1) and bulb-to-bulb distillation (110–115 °C/0.25 Torr) afforded 301 mg (94%) of **1c** as a colorless oil. Data for **1c**: bp 110–115 °C (0.25 Torr); ^1H NMR (300 MHz, $CDCl_3$) 5.19 (t, J = 0.8, 1H, C(4)H), 4.83 (hept, J = 6.2, 1H, $OCH(CH_3)_2$), 2.24 (m, 1H, C(2)CH), 1.62–1.44 (m, 2H, $CH(CH_3)CH_2CH_3$), 1.48–1.40 (four overlapping d, J = 6.2 for each, 6H, $OCH(CH_3)_2$), 1.12 (m, 3H, $CH(CH_3)CH_2CH_3$), 0.86 (m, 3H, CH_2CH_3). (**1c** is an approximate 1/1 mixture of diastereomers, complicating interpretation of the ^1H NMR spectrum); ^{13}C NMR (75.5 MHz, $CDCl_3$) 180.22, 174.45, 132.45, 77.92, 65.88, 31.15, 27.46, 27.31, 23.08, 22.46, 17.62, 17.41, 11.82. (**1c** is an approximate 1/1 mixture of diastereomers, resulting in an apparent doubling of several of the ^{13}C NMR signals); IR (CCl_4) 2970 (m), 2935 (m), 1773 (s), 1627 (s), 1463 (m), 1390 (s), 1378 (m), 1341 (m), 1322 (m), 1102 (m); TLC R_f 0.47 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{11}H_{17}ClO_2$ (MW 216.71): C, 60.97; H, 7.91; Cl, 16.36. Found: C, 61.07; H, 7.88; Cl, 16.27.

2-*t*-Butyl-4-chloro-3-isopropoxy-2-cyclobutenone (1d). Following the general procedure described above, from **10d** (413 mg, 2.10 mmol), Ph_3P (0.74 g, 2.8 mmol, 1.4 equiv), and CCl_4 (1.02 mL, 10.6 mmol, 5.0 equiv) was obtained 0.48 g of crude product. Purification by silica gel chromatography (hexane/EtOAc, 12/1) and bulb-to-bulb distillation (100–105 °C/0.13 Torr) afforded 425 mg (93%) of **1d** as a clear oil which solidified upon cooling. Data for **1d**: bp 100–105 °C (0.13 Torr); mp 40–41 °C; ^1H NMR (300 MHz, $CDCl_3$) 5.19 (s, 1H, C(4)H), 4.83 (hept, J = 6.2, 1H, $CH(CH_3)_2$), 1.45 (d, J = 6.2, 3H, $CH(CH_3)CH_3$), 1.38 (d, J = 6.2, 3H, $CH(CH_3)CH_3$), 1.16 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 179.26, 173.47, 136.46, 78.16, 65.80, 31.35, 27.86, 23.36, 22.52; IR (CCl_4) 2971 (m), 1769 (m), 1624 (s), 1400 (m), 1378 (m), 1345 (m), 1100 (m); TLC R_f 0.52 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{11}H_{17}ClO_2$ (MW 216.71): C, 60.97; H, 7.91; Cl, 16.36. Found: C, 61.07; H, 7.92; Cl, 16.28.

4-Chloro-3-isopropoxy-4-phenyl-2-cyclobutenone (1e). Following the general procedure described above, from **10e** (500 mg, 2.29 mmol), Ph_3P (0.81 g, 3.1 mmol, 1.4 equiv), and CCl_4 (1.10 mL, 11.4 mmol, 5.0 equiv) in CH_3CN (12 mL) was obtained 0.49 g of crude product. Purification by silica gel chromatography (hexane/EtOAc, 8/1) and bulb-to-bulb distillation (175–180 °C/0.30 Torr) afforded 420 mg (77%) of **1e** as a clear glass which solidified upon standing. Data for **1e**: bp 175–180 °C (0.30 Torr); ^1H NMR (300 MHz, $CDCl_3$) 7.76 (d, J = 7.1, 2H, *o*-Ph), 7.40–7.26 (m, 3H, *m*-Ph and *p*-Ph), 5.45 (s, 1H, C(4)H), 5.06 (hept, J = 6.2, 1H, $CH(CH_3)_2$), 1.59 (d, J = 6.2, 3H, $CH(CH_3)CH_3$), 1.50 (d, J = 6.2, 3H, $CH(CH_3)CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 177.81, 172.71, 128.61, 128.52, 128.05, 127.06, 124.90, 79.67, 66.48, 23.53, 22.69; IR (CCl_4) 2986 (m), 1771 (s), 1636 (s), 1600 (m), 1495 (m), 1399 (s), 1378 (m), 1346 (m), 1335 (s), 1096 (m); TLC R_f 0.45 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{13}H_{13}ClO_2$ (MW 236.70): C, 65.97; H, 5.54; Cl, 14.98. Found: C, 65.89; H, 5.52; Cl, 14.91.

2-*n*-Butyl-4-hydroxy-3-methyl-2-cyclobutenone Ethylene Acetal. In a 20-mL round-bottomed flask, a solution of acetal **13a** (200 mg, 1.02 mmol) in Et_2O (3 mL) was cooled to 0 °C (ice/H_2O). To this solution diisobutylaluminum hydride (1.5 M in toluene, 0.82 mL, 1.2 mmol, 1.2 equiv) was added via syringe. After 10 min, the reaction mixture was quenched by the addition of a 1/1 solution of THF/saturated sodium potassium tartrate (10 mL). The cooling bath was removed and the reaction mixture stirred vigorously for 30 min. The reaction mixture was poured into H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The extracts were washed with brine (1 × 20 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. Purification by silica gel chromatography (hexane/EtOAc, 2/1) and bulb-to-bulb distillation (110–115 °C/0.37 Torr) afforded 161 mg (80%) of the acetal as a colorless oil. Data for 2-*n*-butyl-4-hydroxy-3-methyl-2-cyclobutenone ethylene acetal: bp 110–115 °C (0.37 Torr); ^1H NMR (300 MHz, $CDCl_3$) 4.21 (d, J = 10.3, 1H, C(4)H), 3.93 (m, 4H, C(6)H_2 and C(7)H_2), 2.24 (exch d, J = 10.3, 1H, OH), 1.97 (t, J = 7.4, 2H, $C(2)CH_2$), 1.67 (s, 3H, $C(3)CH_3$), 1.40 (m, 2H, $CH_2CH_2CH_3$), 1.28 (m, 2H, CH_2CH_3), 0.84 (t, J = 7.2, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 147.80, 141.67, 110.15, 80.39, 64.81, 64.29, 29.23, 23.57, 22.60, 13.68, 10.31; IR (CCl_4) 3563 (w), 2959 (m), 2933 (m), 1389 (m), 1269 (m), 1108 (m), 1086 (m), 1028 (m), 958 (m); TLC R_f 0.30 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{11}H_{18}O_3$ (MW 198.26): C, 66.64; H, 9.15. Found: C, 66.74; H, 9.12.

3-*n*-Butyl-4-hydroxy-2-methyl-2-cyclobutenone Ethylene Acetal. In a 20-mL round-bottomed flask, a solution of acetal **13b** (365 mg, 1.86 mmol) in Et_2O (6 mL) was cooled to 0 °C (ice/H_2O). To this solution was added diisobutylaluminum hydride (1.5 M in toluene, 1.50 mL, 2.2 mmol, 1.2 equiv) via syringe. After 10 min, the reaction mixture was quenched by the addition of a 1/1 solution of THF/saturated sodium potassium tartrate (20 mL). The cooling bath was removed and the reaction mixture stirred vigorously for 30 min. The reaction mixture was poured into H_2O (30 mL) and extracted with EtOAc (3 × 35 mL). The extracts were washed with brine (1 × 20 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. Purification by silica gel chromatography (hexane/EtOAc, 3/1) and bulb-to-bulb distillation (105–110 °C/0.25 Torr) afforded 300 mg (81%) of the acetal as a colorless oil. Data for 3-*n*-butyl-4-hydroxy-2-methyl-2-cyclobutenone ethylene acetal: bp 105–110 °C (0.25 Torr); ^1H NMR (300 MHz, $CDCl_3$) 4.35 (d, J = 10.6, 1H, C(4)H), 4.00 (m, 4H, C(6)H_2, C(7)H_2), 2.12 (t, J = 7.5, 2H, $C(3)CH_2$), 1.98 (exch d, J = 10.6, 1H, OH), 1.60 (s, 3H, $C(2)CH_3$), 1.48 (m, 2H, $CH_2CH_2CH_3$), 1.33 (m, 2H, CH_2CH_3), 0.90 (t, J = 7.2, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 152.29, 137.32, 109.76, 79.48, 65.08, 64.58, 28.79, 25.11, 22.65, 13.76, 7.80; IR (CCl_4, cm^{-1}) 3563 (w), 2959 (m), 2933 (m), 1445 (w), 1387 (m), 1084 (m); TLC R_f 0.51 (EtOAc). Anal. Calcd for $C_{11}H_{18}O_3$ (MW 198.26): C, 66.64; H, 9.15. Found: C, 66.46; H, 9.17.

2-*n*-Butyl-4-hydroxy-3-methyl-2-cyclobuten-1-one (14a). In a 100-mL round-bottomed flask, a solution of acetal **13a** (520 mg, 2.65 mmol) in Et_2O (8 mL) was cooled to 0 °C (ice/H_2O). To this solution was added diisobutylaluminum hydride (1.5 M in toluene, 2.12 mL, 3.2 mmol, 1.2 equiv) via syringe. After 15 min, the reaction mixture was quenched by the addition of 1 N HCl (5 mL). The cooling bath was removed and the reaction mixture stirred vigorously for 60 min. The reaction mixture was poured into H_2O (30 mL) and extracted with EtOAc (3 × 40 mL). The extracts were washed with brine (1 × 30 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. The residue was dissolved in THF (10 mL) and treated with 3 N HCl (2 mL). The reaction mixture was stirred for 45 min, poured into saturated $NaHCO_3$ (25 mL), and extracted with EtOAc (3 × 30 mL). The extracts were washed with brine (1 × 30 mL), dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to a colorless oil. Purification by silica gel chromatography (hexane/EtOAc, 3/1) and bulb-to-bulb distillation (135–140 °C/0.39 Torr) afforded 325 mg (80%) of **14a** as a colorless oil. Data for **14a**: bp 135–140 °C (0.39 Torr); ^1H NMR (300 MHz, $CDCl_3$) 4.95 (s, 1H, C(4)H), 4.80 (exch s, 1H, OH), 2.13 (s, 3H, $C(3)CH_3$), 2.04 (t, J = 7.6, 2H, $C(2)CH_2$), 1.41 (m, 2H, $CH_2CH_2CH_3$), 1.22 (m, 2H, CH_2CH_3), 0.81 (t, J = 7.3, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 194.31, 176.55, 151.97, 84.69, 28.57, 22.68, 22.33, 13.47, 12.51; IR (CCl_4, cm^{-1}) 3394 (br m), 2962 (m), 2934 (m), 1752 (s), 1636 (m), 1380 (m), 1090 (m), 1013 (m); TLC R_f 0.18 (hexane/EtOAc, 2/1); HRMS Calcd for $C_9H_{14}O_2$ (MW 154.21): 154.0993726. Found: 154.0993798.

3-*n*-Butyl-4-hydroxy-2-methyl-2-cyclobuten-1-one (14b). In a 100-mL round-bottomed flask, a solution of acetal **13b** (1.005 g, 5.12 mmol) in Et_2O (20 mL) was cooled to 0 °C (ice/H_2O). To this solution diisobutylaluminum hydride (1.5 M in toluene, 4.10 mL, 6.1 mmol, 1.2 equiv) was added via syringe. After 15 min, the reaction mixture was quenched by the addition of 1 N HCl (10 mL). The cooling bath was removed and the reaction mixture stirred vigorously for 10 min. The reaction mixture was poured into 1 N HCl (30 mL) and extracted with EtOAc (3 × 70 mL). The extracts were washed with brine (1 × 50 mL), combined,

dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. The residue was dissolved in THF (25 mL) and treated with 3 N HCl (4 mL). The reaction mixture was stirred for 20 min, poured into saturated $NaHCO_3$ (40 mL), and extracted with EtOAc (3 × 80 mL). The extracts were washed with brine (1 × 40 mL), dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to a colorless oil. Purification by silica gel chromatography (hexane/EtOAc, 4/1) and bulb-to-bulb distillation (140–145 °C/0.27 Torr) afforded 728 mg (92%) of **14b** as a colorless oil. Data for **14b**: bp 140–145 °C (0.27 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) 5.09 (s, 1H, C(4)H), 2.9 (exch br, 1H, O*H*), 2.58 (t, J = 7.4, 2H, C(3)CH_2), 1.72 (s, 3H, C(2)CH_3), 1.64 (m, 2H, CH_2-CH_2CH_3), 1.40 (hex, J = 7.4, 2H, CH_2CH_3), 0.95 (t, J = 7.3, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 194.17, 180.46, 147.61, 84.19, 28.05, 27.12, 22.78, 13.68, 7.63; IR (CCl_4, cm^{-1}) 3392 (m), 2961 (m), 2934 (m), 1752 (s), 1634 (s), 1102 (m); TLC R_f 0.18 (hexane/EtOAc, 1/1); HRMS Calcd for $C_9H_{14}O_2$ (MW 154.21): 154.0993726. Found: 154.0993798.

2-*n*-Butyl-4-chloro-3-methyl-2-cyclobutenone (3a). Following the general procedure described above, from **14a** (1.240 g, 8.04 mmol), Ph_3P (2.74 g, 10.4 mmol, 1.34 equiv), and CCl_4 (3.88 mL, 40.2 mmol, 5.00 equiv) in CH_3CN (32 mL) was obtained a clear oil. Purification by silica gel chromatography (hexane/EtOAc, 16/1) and bulb-to-bulb distillation (85–90 °C/0.15 Torr) afforded 1.257 g (91%) of **3a** as a colorless oil. Data for **3a**: bp 85–90 °C (0.15 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) 5.15 (s, 1H, C(4)H), 2.18 (s, 3H, C(3)CH_3), 2.12 (m, 2H, C(2)CH_2), 1.47 (m, 2H, C$H_2CH_2CH_3$), 1.30 (m, 2H, CH_2CH_3), 0.88 (t, J = 7.3, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$); 184.33, 171.08, 153.03, 70.16, 28.47, 23.36, 22.44, 13.57, 12.49; IR (CCl_4) 2962 (m), 2935 (m), 1781 (s), 1640 (s), 1432 (m), 1383 (m), 1218 (m); TLC R_f 0.58 (hexane/EtOAc, 2/1); HRMS calcd for $C_9H_{13}ClO$ (MW 172.66): 172.0654870. Found: C, 172.0654929.

3-*n*-Butyl-4-chloro-2-methyl-2-cyclobutenone (3b). Following the general procedure described above for **1b**, from **14b** (560 mg, 3.63 mmol), Ph_3P (1.28 g, 4.88 mmol, 1.34 equiv), and CCl_4 (1.75 mL, 18.1 mmol, 5.00 equiv) in CH_3CN (18 mL) was obtained a clear oil. Purification by silica gel chromatography (hexane/EtOAc, 24/1), and bulb-to-bulb distillation (75–80 °C/0.16 Torr) afforded 512 mg (82%) of **3b** as a colorless oil. Data for **3b**: bp 75–80 °C (0.16 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) 5.18 (q, J = 0.5, 1H, C(4)H), 2.56 (m, 2H, C(3)CH_2), 1.73 (d, J = 0.5, 3H, C(2)CH_3), 1.65 (m, 2H, C$H_2CH_2CH_3$), 1.38 (m, 2H, CH_2CH_3), 0.93 (t, J = 7.3, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 184.38, 175.26, 148.25, 68.87, 27.74, 26.82, 22.65, 13.57; 8.15 (CH_2CH_3); IR (CCl_4, cm^{-1}) 2964 (m), 2934 (m), 1783 (s), 1638 (m); TLC R_f 0.53 (hexane/EtOAc, 2/1). Anal. Calcd for $C_9H_{13}ClO$ (MW 172.66): C, 62.61; H, 7.59; Cl, 20.53. Found: C, 62.65; H, 7.56; Cl, 20.62.

2,4-Di-*n*-butyl-4-hydroxy-3-isopropoxy-2-cyclobuten-1-one (15a). In a 100 mL two-necked flask, a solution of dione **9b** (1.25 g, 6.37 mmol) in THF (25 mL) was cooled to −78 °C (CO_2/IPA). To this solution was added *n*-BuLi (2.68 M in hexane; 2.38 mL, 6.38 mmol, 1.00 equiv) via syringe pump over a 35-min period. The reaction mixture was stirred an additional 60 min at −78 °C and quenched with 1/1 H_2O/THF (10 mL). The reaction mixture was stirred at −78 °C for 20 min, allowed to warm to room temperature, poured into H_2O (40 mL), and extracted with Et_2O (3 × 70 mL). The extracts were washed with brine (1 × 50 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to a yellow oil. Purification by silica gel chromatography (hexane/EtOAc, 3/1) and bulb-to-bulb distillation (170–175 °C/0.42 Torr) afforded 1.203 g (75%) of **15a** as a colorless oil. Data for **15a**: bp 170–175 °C (0.42 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) 4.80 (hept, J = 6.2, 1H, CH(CH_3)$_2$), 4.05 (exch s, 1H, O*H*), 2.04 (m, 2H, C(2)CH_2), 1.87 (m, 1H, C(4)CH_a), 1.77 (m, 1H, C(4)CH_b), 1.49–1.18 (m, 8H, C$H_2CH_2CH_3$, 2 sets), 1.39 (apparent t, J = 6.2, 6H, CH(CH_3)$_2$), 0.87 (t, J = 7.2, 3H, CH_2CH_3), 0.85 (t, J = 7.2, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 194.32, 182.45, 126.15, 91.45, 76.55, 32.58, 29.54, 27.25, 22.74, 22.68, 22.54, 22.03, 13.83, 13.65; IR (CCl_4, cm^{-1}) 3595 (br m), 2961, (m), 1746 (m), 1613 (s), 1596 (s), 1386 (s), 1339 (m), 1104 (s); TLC R_f 0.25 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{15}H_{26}O_3$ (MW 232.28): C, 70.83; H, 10.30. Found: C, 70.70; H, 10.33.

4-Hydroxy-3-isopropoxy-4-methyl-2-phenyl-2-cyclobuten-1-one (15b). A 100-mL three-necked flask was fitted with an addition funnel, septum, and gas inlet. The flask was charged with dione **9e** (1.215 g, 5.62 mmol), THF (18 mL), and Et_2O (12 mL). The reaction mixture was cooled to −78 °C (CO_2/IPA). To this yellow solution was added CH_3Li (1.25 M in Et_2O, 4.50 mL, 5.62 mmol) dropwise via addition funnel over a 20-min period. After 30 min, the reaction mixture was quenched with 1/1 THF/H_2O (20 mL), allowed to warm to room temperature, and poured into H_2O (40 mL). The product was extracted with Et_2O (3 × 50 mL), and the extracts were washed with brine (1 × 40 mL). The combined extracts were dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to an off-white solid (1.12 g). Purification by silica gel chromatography (hexane/EtOAc, 3/1) and recrystallization (Et_2O/pentane) afforded 1.048 g (80%) of the alcohol **15b** as white crystals. Data for **15b**: mp 150–151 °C (Et_2O/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 7.74 (d, J = 7.1, 2H, *o*-Ph), 7.30 (m, 3H, *o*-Ph, *p*-Ph), 5.24 (hept, J = 6.1, 1H, CH(CH_3)$_2$), 4.94 (exch s, 1H, O*H*), 1.79 (s, 3H, C(4)CH_3), 1.59 (d, J = 6.1, 3H, CH(CH_3)CH_3), 1.56 (d, J = 6.1, 3H, CH(CH_3)CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 192.20, 182.97, 128.96, 128.32, 127.71, 122.00, 89.40, 78.62, 23.32, 23.02, 20.60; IR (CCl_4, cm^{-1}) 3570 (br w), 1750 (m), 1737 (m), 1629 (s), 1596 (s), 1495 (m), 1399 (s), 1333 (m), 1086 (m); TLC R_f 0.23 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{14}H_{16}O_3$ (MW 232.28): C, 72.39; H, 6.94. Found: C, 72.39; H, 6.98.

2,4-Di-*n*-butyl-4-chloro-3-isopropoxy-2-cyclobutenone (4a). In a 50-mL round-bottomed flask, a solution of alcohol **15a** (620 mg, 2.44 mmol) in CH_3CN (11 mL) was treated with Ph_3P (1.28 g, 4.88 mmol, 2.00 equiv) and Et_4NCl (20 mg). The reaction vessel was placed in a water bath and CCl_4 (1.41 mL, 14.6 mmol, 6.0 equiv) was added via syringe. After 48 h, CH_3OH (4 mL) was added. The reaction mixture was stirred an additional 10 min and concentrated to a yellow oil. The residue was dissolved in a minimum of CH_2Cl_2 (3 mL) and applied to a pad of silica gel (40 × 40 mm). The pad was rinsed with 8/1 hexane/EtOAc (200 mL). The eluent was concentrated and the residue purified by silica gel chromatography (hexane/EtOAc, 60/1) and bulb-to-bulb distillation (140–145 °C/0.28 Torr) to afford 498 mg (75%) of **4a** as a clear oil. Data for **4a**: bp 140–145 °C (0.28 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) 4.79 (hept, J = 6.1, 1H, OC*H*), 2.11–1.94 (m, 4H, C(2)CH_2, C(4)CH_2)), 1.55–1.49 (m, 2H, C(4)CH_2CH_2), 1.42 (app t, J = 6.1, 6H, OCH(CH_3)$_2$), 1.38–1.23 (m, 6H, C(2)-CH_2CH_2CH_2, C(4)(CH_2)$_2$CH_2), 0.90–0.83 (m, 6H, 2 CH_3's); ^{13}C NMR (75.5 MHz, $CDCl_3$) 185.74, 171.37, 124.61, 82.63, 76.95, 35.50, 29.54, 27.67, 22.73, 22.50, 22.40, 22.25, 13.67, 13.61; IR (CCl_4, cm^{-1}) 2962 (m), 2935 (m), 1773 (s), 1619 (s), 1387 (s), 1341 (w), 1320 (w), 1104 (m); TLC R_f 0.24 (hexane/EtOAc, 8/1). Anal. Calcd for $C_{15}H_{25}ClO_2$ (MW 218.76): C, 66.04; H, 9.24; Cl, 13.00. Found: C, 65.81; H, 9.18; Cl, 12.85.

4-Chloro-4-methyl-3-isopropoxy-2-phenyl-2-cyclobutenone (4b). In a 50-mL round-bottomed flask, a suspension of **15b** (410 mg, 1.76 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C (ice/H_2O). To this suspension was added pyridine (1.42 mL, 17.6 mmol, 10.0 equiv) followed immediately by $SOCl_2$ (450 μL, 6.17 mmol, 3.50 equiv). After 30 min, the reaction mixture was poured onto a prewetted pad of silica gel (60 × 40 mm) and eluted with 8/1 hexane/EtOAc (200 mL). The elutent was concentrated to a white solid (0.39 g). Recrystallization (hexane) afforded 314 mg (71%) of **4b** as white needles. Data for **4b**: mp 80–82 °C dec (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 7.74 (m, 2H, *o*-Ph), 7.40–7.27 (m, 3H, *m*,*p*-Ph), 5.18 (hept, J = 6.2, 1H, OC*H*), 2.00 (s, 3H, C(2)CH_3), 1.58 (d, J = 6.2, 3H, OCH(CH_3)CH_3), 1.53 (d, J = 6.2, 3H, OCH(CH_3)CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 182.35, 177.04, 128.49; 128.40; 128.25; 127.11, 121.67; 79.72, 79.17, 23.86, 23.28, 22.92; IR (CCl_4, cm^{-1}) 1779 (m), 1632 (s), 1601 (m), 1395 (s), 1335 (m), 1088 (m); TLC R_f 0.51 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{14}H_{15}ClO_2$ (MW 250.73): C, 67.07; H, 6.03; Cl, 14.14. Found: C, 67.16; H, 6.08; Cl, 14.08.

4-Hydroxy-3-isopropoxy-2,4-dimethyl-2-cyclobutenone. In a 50-mL two-necked flask a solution of dione **9a** (500 mg, 3.24 mmol) in THF (13 mL) was cooled to −78 °C (CO_2/IPA). To this solution was added CH_3Li (1.43 M in Et_2O, 2.30 mL, 3.29 mmol, 1.01 equiv) via syringe pump over a 25-min period. The reaction mixture was stirred an additional 60 min at −78 °C and quenched with saturated NH_4Cl (4 mL). The reaction mixture was allowed to warm to room temperature, poured into H_2O (25 mL), and extracted with Et_2O (3 × 40 mL). The extracts were washed

with brine (1 × 30 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to a yellow oil (0.51 g). The residue was purified by silica gel chromatography (Et_2O/hexane, 2/1) and bulb-to-bulb distillation (140–145 °C/0.52 Torr) to afford 299 mg (54%) of the alcohol as a clear oil which solidified upon standing. Data for 4-hydroxy-3-isopropoxy-2,4-dimethyl-2-cyclobutenone: bp 140–145 °C (0.52 Torr); mp 60–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 4.84 (hept, J = 6.2, 1H, OC*H*), 4.09 (br exch, 1H, OH), 1.62 (s, 3H, C(4)CH_3), 1.49 (s, 3H, C(2)-CH_3), 1.41 (d, J = 6.2, 6H, OCH(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 195.16, 184.08, 119.81, 87.99, 76.56, 22.61, 22.57, 19.20, 6.58; IR (CCl_4, cm^{-1}) 3336 (br w), 2985 (w), 1754 (m), 1620 (s), 1389 (s), 1335 (m), 1316 (m), 1144 (m), 1105 (s); TLC R_f 0.08 (hexane/EtOAc, 2/1). Anal. Calcd for $C_9H_{14}O_3$ (MW 170.21): C, 63.51; H, 8.29. Found: C, 63.36; H, 8.26.

4-Chloro-3-isopropoxy-2,4-dimethyl-2-cyclobutenone. In a 50-mL round-bottomed flask, a solution of 4-hydroxy-3-isopropoxy-2,4-dimethylcyclobutenone (290 mg, 1.70 mmol) in CH_3CN (9 mL) was treated with Ph_3P (0.89 g, 3.4 mmol, 2.0 equiv) and Et_4NCl (20 mg). The reaction vessel was placed in a water bath and CCl_4 (0.98 mL, 10 mmol, 6.0 equiv) was added via syringe. After 48 h, CH_3OH (4 mL) was added. The reaction mixture was stirred an additional 10 min and concentrated to a yellow oil. The residue was dissolved in a minimum of CH_2Cl_2 (3 mL) and applied to a pad of silica gel (40 × 40 mm). The pad was rinsed with 6/1 hexane/EtOAc (150 mL). The eluent was concentrated and the residue purified by silica gel chromatography (hexane/EtOAc, 8/1) followed by bulb-to-bulb distillation (100–105 °C/0.4 Torr) to afford 241 mg (75%) of 4-chloro-3-isopropoxy-2,4-dimethyl-2-cyclobutenone as a clear oil. Data for 4-chloro-3-isopropoxy-2,4-dimethylcyclobutenone: bp 100–105 °C (0.4 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) 4.84 (hept, J = 6.1, 1H, OC*H*), 1.74 (app t, J = 2.0, 3H, C(2)CH_3 or C(4)CH_3), 1.70 (app t, J = 1.8, 3H, C(4)CH_3 or C(2)CH_3), 1.45 (d, J = 6.1, 3H, OCHC$_a$$H_3$), 1.43 (d, J = 6.1, 3H, OCHC$_b$$H_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 185.95, 178.70, 118.09, 78.47, 76.91, 22.19, 22.04, 21.86, 6.98; IR (CCl_4, cm^{-1}) 2986 (m), 1786 (s), 1622 (s), 1440 (m), 1400 (s), 1390 (s), 1340 (m), 1320 (m), 1103 (s); TLC R_f 0.40 (hexane/EtOAc, 2/1). Anal. Calcd for $C_9H_{13}ClO_2$ (MW 188.66): C, 57.30 H, 6.95; Cl, 18.79. Found: C, 57.35; H, 6.98; Cl, 18.72.

3-(Tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione 2-(Ethylene acetal) (5). In a 100 mL three-necked flask fitted with an addition funnel, a suspension of CuCN (515 mg, 5.75 mmol, 1.15 equiv) in THF (10 mL) was cooled to −78 °C (CO_2/IPA). To this suspension was added *n*-BuLi (2.45 M in hexane; 4.70 mL, 11.5 mmol, 2.30 equiv) via syringe. The reaction mixture was warmed to 0 °C (ice/H_2O) and stirred vigorously until all solids had dissolved (~5 min). The reaction vessel was recooled to −78 °C and tri-*n*-butyl(trimethylsilyl)stannane (2.10 g, 5.78 mmol, 1.16 equiv) was added via syringe. The reaction mixture was stirred 15 min at −78 °C, the cooling bath was removed, and the reaction mixture was stirred for 90 min. The resulting black suspension was cooled to −78 °C. A solution of **12d** (921 mg, 5.00 mmol) in THF (5 mL) was added to the reaction mixture dropwise via addition funnel over a 10 min-period, and the addition funnel was rinsed with THF (1 mL). The reaction mixture was stirred 1 h at −78 °C, and quenched by the dropwise addition of saturated NH_4Cl (20 mL). The reaction mixture was allowed to warm to room temperature, poured into H_2O (40 mL), and extracted with EtOAc (3 × 100 mL). The extracts were washed with H_2O (1 × 60 mL) and brine (1 × 60 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to a golden oil. The crude material was dried under vacuum (0.3 Torr) until the ^{1}H NMR spectrum of an aliquot of material showed no isopropoxy signals (16 h). The residue was purified by silica gel chromatography (hexane/EtOAc, 20/1) to afford 1.66 g (80%) of the stannane **5** as a golden yellow liquid. Data for **5**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.13 (t, $^3J_{Sn-H}$ = 5.0, 1H, C(3)H), 4.18–4.03 (m, 4H, OCH_2CH_2O), 1.63–1.49 (m, 6H, C$H_2$$CH_2CH_3$), 1.31 (app hex, J = 7.3, 6H, CH_2CH_3), 1.09 (t of t, $^2J_{Sn-H}$ = 26.3, $^2J_{H-H}$ = 7.3, 6H, CH_2Sn), 0.89 (t, J = 7.2, 9H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 199.07, 195.54, 161.13, 66.16, 28.90, 27.12, 13.57, 10.14; IR (CCl_4, cm^{-1}) 2960 (m), 2925 (m), 2875 (w), 2856 (w), 1765 (s), 1260 (m), 1044 (m), 1013 (m), 751 (s); TLC R_f 0.55 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{18}H_{32}O_3Sn$ (MW 415.14) C, 52.08; H, 7.77. Found: C, 52.20; H, 7.84.

General Procedure for the Preparation of Benzocyclobutenedione Monoacetals 6: 3-Hydroxy-5-isopropoxy-4-methylbenzocyclobutenedione 1-(Ethylene acetal) (6a). The preparation of 3-hydroxy-5-isopropoxy-4-methylbenzocyclobutenedione 1-(ethylene acetal) (**6a**) will serve to illustrate the general procedure for the preparation of **6a–j**.

In a 25-mL two-necked flask, a solution of **1a** (624 mg, 3.57 mmol) and **5** (1.52 g, 3.70 mmol, 1.02 equiv) in THF (15 mL) was degassed (3 freeze/purge/thaw cycles). To the reaction mixture was added $(PhCN)_2PdCl_2$ (13 mg, 0.034 mmol, 1 mol%) and tris-(2-furyl)phosphine (16 mg, 0.07 mmol, 2 mol%). The reaction mixture was degassed a final time, and stirred at room temperature for 30 min. The reaction mixture was heated to 55–60 °C (bath temperature) for 3 h, cooled to room temperature, and poured into Et_2O (100 mL). The ethereal layer was washed with H_2O (1 × 40 mL) and brine (1 × 50 mL). The aqueous layers were extracted with Et_2O (2 × 80 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, through a pad of Celite, and concentrated. The residue was dissolved in CH_3CN (50 mL) and washed with hexane (4 × 50 mL). The washings were extracted with CH_3CN (1 × 50 mL). The combined CH_3CN layers were concentrated, and the residue was purified by silica gel chromatography (hexane/EtOAc, 4/1) to afford 897 mg (95%) of **6a** as a white solid. The analytical sample was obtained by recrystallization from Et_2O/hexane. Data for **6a**: mp 148–148.5 °C (Et_2O/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 7.66 (exch s, 1H, O*H*), 6.73 (s, 1H, C(6)H), 4.67 (hept, J = 6.0, 1H, C*H*(CH_3)$_2$), 4.25 (m, 4H, OCH_2CH_2O), 2.08 (s, 3H, C(4)CH_3), 1.39 (d, J = 6.0, 6H, CH(CH_3)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 189.99, 165.67, 157.66, 149.01, 128.94, 118.65, 118.57, 97.17, 71.41, 66.37, 22.01, 8.70; IR (CCl_4) 3330 (br w), 2983 (w), 1757 (m), 1736 (w), 1607 (m), 1431 (w), 1337 (w), 1320 (m), 1218 (m), 1135 (m), 1027 (m); TLC R_f 0.35 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{14}H_{16}O_5$ (MW 264.28): C, 63.63; H, 6.10. Found: C, 63.48; H, 6.08.

4-*n*-Butyl-3-hydroxy-5-isopropoxybenzocyclobutenedione 1-(Ethylene acetal) (6b). Following the general procedure described above for the preparation of **6a**, from stannylcyclobutenone **5** (290 mg, 0.70 mmol), 4-chlorocyclobutenone **1b** (160 mg, 0.74 mmol, 1.1 equiv), $(PhCN)_2PdCl_2$ (3 mg, 0.007 mmol, 1 mol%), and tris-(2-furyl)phosphine (3.5 mg, 0.0015 mmol, 2 mol%) an orange oil was obtained. Purification by silica gel chromatography (hexane/EtOAc, 4/1) afforded 212 mg (99%) of **6b** as white crystals. Recrystallization (Et_2O/hexane) provided the analytical sample. Data for **6b**: mp 145–146 °C (Et_2O/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 8.31 (exch s, 1H, O*H*), 6.72 (s, 1H, C(6)H), 4.66 (hept, J = 6.0, 1H, C*H*(CH_3)$_2$), 4.25 (m, 4H, OCH_2CH_2O), 2.61 (m, 2H, C(4)CH_2), 1.37 (d, J = 6.0, 6H, CH-(CH_3)$_2$), 1.46–1.30 (m, 4H, CH_2C$H_2$$CH_3$), 0.91 (t, J = 7.0, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 189.03, 165.35, 157.72, 148.78, 129.29, 123.46, 118.61, 97.22, 71.07, 66.34, 30.67, 22.86, 22.63, 21.89, 13.91; IR (CCl_4, cm^{-1}) 3340 (br w), 1757 (m), 1736 (m), 1605 (m), 1431 (w), 1318 (m), 1213 (s), 1136 (m), 1113 (w), 1026 (m); TLC R_f 0.18 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{17}H_{22}O_5$ (MW 306.36): C, 66.65; H, 7.24. Found: C, 66.57; H, 7.26.

4-*s*-Butyl-3-hydroxy-5-isopropoxybenzocyclobutenedione 1-(Ethylene acetal) (6c). Following the general procedure described above for the preparation of **6a**, from stannylcyclobutenone **5** (595 mg, 1.43 mmol), 4-chlorocyclobutenone **1c** (299 mg, 1.38 mmol, 1.1 equiv), $(PhCN)_2PdCl_2$ (5.3 mg, 0.014 mmol, 1.0 mol%), and tris(2-furyl)phosphine (6.4 mg, 0.028 mmol, 2.0 mol%) an orange oil was obtained. Purification by silica gel chromatography (hexane/EtOAc, 3/1) afforded 384 mg (91%) of **6c** as a white foam. Data for **6c**: mp 61–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.87 (exch s, 1H, O*H*), 6.70 (s, 1H, C(6)H), 4.67 (hept, J = 6.1, 1H, C*H*(CH_3)$_2$), 4.24 (m, 4H, OCH_2CH_2O), 3.32 (m, 1H, C(4)C*H*), 1.90–1.75 (m, 1H, C(4)CHC$H_a$$H_b$), 1.60 (app hept, J = 7.1, 2H, C(4)CHC$H_a$$H_b$), 1.38 (d, J = 6.1, 6H, OCH-(CH_3)$_2$), 1.24 (d, J = 7.1, 3H, C(4)CHCH_3), 0.76 (t, J = 7.4, 3H, C(4)CHCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 190.05, 166.16, 157.70, 149.53, 129.47, 126.29, 118.63, 97.44, 71.08, 66.36, 31.54, 27.09, 21.88, 18.13, 12.74; IR (CCl_4) 3336 (br w), 1966 (m), 1758 (m), 1735 (m), 1603 (s), 1428 (m), 1318 (m), 1216 (m), 1138 (m), 1111 (m), 1027 (s); TLC R_f 0.32 (hexane/EtOAc, 2/1). HRMS Calcd for $C_{17}H_{22}O_5$ (MW 306.36): 306.1467117. Found: 306.1467241.

4-*tert*-Butyl-3-hydroxy-5-isopropoxybenzocyclobutenedione 1-(Ethylene acetal) (6d). Following the general procedure described above for the preparation of **6a** (except using dioxane as solvent and heating to 110 °C instead of 60 °C), from stannylcyclobutenone **5** (392 mg, 0.94 mmol, 1.05 equiv), 4-chlorocyclobutenone **1d** (195 mg, 0.90 mmol), $(PhCN)_2PdCl_2$ (8 mg, 0.02 mmol, 2 mol%), and tris(2-furyl)phosphine (9 mg, 0.04 mmol, 4 mol%) was obtained an orange oil. Purification by silica gel chromatography (hexane/EtOAc, 4/1) afforded two products: 28 mg of 2-chloroethyl (4-*tert*-butyl-5-hydroxy-3-isopropoxy)benzoate (**17**) (10%) as white crystals and 190 mg (69%) of **6d** as a colorless glass. Data for **6d**: ^{1}H NMR (300 MHz, $CDCl_3$) 6.71 (s, 1H, C(6)H), 6.60 (exch s, 1H, O*H*), 4.73 (hept, J = 6.1, 1H, $OCH(CH_3)_2$), 4.24 (m, 4H, OCH_2CH_2O), 1.48 (s, 9H, $C(4)C(CH_3)_3$), 1.42 (d, J = 6.1, 6H, $OCH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 190.12, 167.06, 157.45, 150.24, 130.80, 127.82, 118.83, 97.91, 71.21, 66.34, 36.67, 31.40, 21.74; IR (CCl_4, cm^{-1}) 3567 (br w), 2981 (w), 1756 (m), 1603 (m), 1420 (m), 1340 (m), 1306 (m), 1254 (w), 1185 (m), 1160 (m), 1111 (m), 1067 (w), 1025 (m); TLC R_f 0.23 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{17}H_{22}O_5$ (MW 306.36): C, 66.65, H: 7.24. Found: C: 66.47, H: 7.33. Data for **17**: mp 89–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.13 (d, J = 1.5, 1H, C(2)H or C(6)H), 7.03 (d, J = 1.5, 1H, C(2)H or C(6)H), 5.38 (s, 1H, OH), 4.67 (hept, J = 6.0, 1H, $OCH(CH_3)_2$), 4.54 (t, J = 5.6, 2H, $C(1)CO_2CH_2$), 3.79 (t, J = 5.6, 2H, CH_2Cl), 1.53 (s, 9H, $C(5)C(CH_3)_3$), 1.36 (d, J = 6.0, 6H, $OCH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 166.02, 157.82, 155.38, 127.47, 111.15, 107.12, 70.02, 64.42, 41.66, 31.47, 21.86; IR (CCl_4) 3607 (w), 2980 (w), 1726 (m), 1410 (m), 1385 (w), 1341 (w), 1327 (w), 1266 (w), 1198 (w), 1063 (w); TLC R_f 0.423 (hexane/EtOAc, 2/1); HRMS calcd for $C_{16}H_{23}ClO_4$ (MW 314.81) 314.1284871, found 314.128872.

3-Hydroxy-5-isopropoxy-4-phenylbenzocyclobutenedione 1-(Ethylene acetal) (6e). Following the general procedure described above for the preparation of **6a**, from stannylcyclobutenone **5** (556 mg, 1.34 mmol, 1.04 equiv), 4-chlorocyclobutenone **1e** (306 mg, 1.29 mmol), $(PhCN)_2PdCl_2$ (5 mg, 0.01 mmol, 1 mol%), and tris(2-furyl)phosphine (6 mg, 0.02 mmol, 2 mol%) an orange oil was obtained. Purification by silica gel chromatography (hexane/EtOAc, 3/1) and recrystallization (EtOAc/hexane) afforded 379 mg (90%) of **6e** as granular white crystals. Data for **6e**: mp 194–197 °C dec (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 7.45 (m, 3H, *o,p*-Ph), 7.27 (m, 2H, *m*-Ph), 6.82 (s, 1H, C(6)H), 6.60 (exch s, 1H, OH), 4.62 (hept, J = 6.1, 1H, $CH(CH_3)_2$), 4.27 (m, 4H, OCH_2CH_2O), 1.25 (d, J = 6.1, 6H, $CH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 188.93, 164.25, 164.25; 160.04; 159.04; 148.24; 131.36, 130.45; 128.77; 128.16; 119.10, 97.94, 71.86, 66.47, 21.71; IR (CCl_4) 3509 (br w), 1753 (s), 1737 (m), 1594 (s), 1322 (m), 1140 (s), 1027 (s); TLC R_f 0.20 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{19}H_{18}O_5$ (MW 326.35): C, 69.93; H, 5.56. Found: C, 69.71; H, 5.57.

4,5-Diethyl-3-hydroxybenzocyclobutenedione 1-(Ethylene acetal) (6f). Following the general procedure described above for the preparation of **6a**, from stannylcyclobutenone **5** (606 mg, 1.46 mmol, 1.04 equiv), 4-chlorocyclobutenone **2** (222 mg, 1.40 mmol), $(PhCN)_2PdCl_2$ (5.4 mg, 0.014 mmol, 1 mol%), and tris(2-furyl)phosphine (6.5 mg, 0.028 mmol, 2 mol%) was obtained an orange oil. Purification by silica gel chromatography (hexane/EtOAc, 4/1) afforded 210 mg (61%) of **6f** as a white solid. Recrystallization (hexane) afforded the analytical sample. Data for **6f**: mp 129.5–130.5 °C (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 8.05 (br exch s, 1H, OH), 7.12 (s, 1H, C(6)H), 4.26 (m, 4H, OCH_2CH_2O), 2.82–2.67, (m, 4H, $C(4)CH_2$, $C(5)CH_2$), 1.25 (t, J = 7.5, 3H, $C(5)CH_2CH_3$), 1.12 (t, J = 7.5, 3H, $C(4)CH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 192.40, 155.93, 155.57, 147.42, 133.93, 133.18, 118.95, 113.95, 66.41, 27.16, 18.90, 15.03, 13.70; IR (CCl_4, cm^{-1}) 3550 (w), 3365 (br w), 2973 (m), 1758 (s), 1603 (m), 1299 (m), 1023 (m); TLC R_f 0.38 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{14}H_{16}O_4$ (MW 248.28): C, 67.73; H, 6.50. Found: C, 67.81; H, 6.53.

3-Hydroxy-4-methyl-5-phenylbenzocyclobutenedione 1-(Ethylene acetal) (6g). Following the general procedure described above for the preparation of **6a** (except heating to only 55 °C), from stannylcyclobutenone **5** (356 mg, 0.86 mmol, 1.04 equiv), 4-chlorocyclobutenone **3c** (159 mg, 0.83 mmol), $(PhCN)_2PdCl_2$ (5.0 mg, 0.013 mmol, 1.6 mol%), and tris(2-furyl)phosphine (6.2 mg, 0.026 mmol, 3.2 mol%) an orange oil was obtained. Purification by silica gel chromatography (hexane/EtOAc, 3/1) and recrystallization (CH_2Cl_2/hexane) afforded 130 mg (56%) of **6g** as white crystals. Note: compound **6g** is prone to palladium-catalyzed ring-opening to compounds of type **17**. Strict control of reaction temperature (no higher than 55 °C for 2 h) is required. Data for **6g**: mp 174–176 °C dec (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 7.43 (m, 2H, *m*-Ph), 7.30–7.24 (m, 3H, *o,p*-Ph), 7.17 (s, 1H, C(6)H), 7.11 (exch s, 1H, OH), 4.25 (m, 4H, OCH_2CH_2O), 2.14 (s, 3H, $C(4)CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 192.53, 155.86, 153.86, 147.74, 140.98, 134.54, 128.66, 128.26, 127.76, 127.13, 119.21, 115.72, 66.49, 13.36; IR (CCl_4, cm^{-1}) 3550 (br w), 2900 (w), 1762 (s), 1603 (m), 1416 (s), 1349 (m), 1306 (w), 1154 (m), 1026 (m); TLC R_f 0.32 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{17}H_{14}O_4$ (MW 282.30): C: 72.33, H: 5.00. Found: C, 72.28, H: 5.06.

3-Hydroxy-5-methyl-4-phenylbenzocyclobutenedione 1-(Ethylene acetal) (6h). Following the general procedure described above for the preparation of **6a**, from stannylcyclobutenone **5** (460 mg, 1.11 mmol, 1.01 equiv), 4-chlorocyclobutenone **3d** (206 mg, 1.19 mmol), Pd_2dba_3 (14 mg, 0.015 mmol, 1 mol%), and tris(2-furyl)phosphine (14 mg, 0.060 mmol, 5 mol%) an orange oil was obtained. Purification by silica gel chromatography (hexane/EtOAc, 3/1) and recrystallization ($CHCl_3$/hexane) afforded 215 mg (75%) of **6h** as white plates. Data for **6h**: mp 165–168 °C dec ($CHCl_3$/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 7.55–7.45 (m, 3H, *m,p*-Ph), 7.26–7.20 (m, 3H, *o*-Ph, C(6)H), 6.06 (br exch s, 1H, OH), 4.25 (m, 4H, OCH_2CH_2O), 2.16 (s, 3H, $C(5)CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 190.79, 158.54, 149.31, 146.40, 133.76, 131.98, 129.80, 129.76, 129.47, 128.60, 119.40, 115.47, 66.51, 22.20; IR (CCl_4, cm^{-1}) 3530 (br w), 1773 (m), 1613 (w), 1312 (w), 1278 (w), 1044 (w), 1026 (w); TLC R_f 0.34 (hexane/EtOAc, 2/1); HRMS Calcd for $C_{17}H_{14}O_4$ (MW 282.30): 282.08920908. Found: 282.0892091.

5-*n*-Butyl-3-hydroxy-4-methylbenzocyclobutenedione 1-(Ethylene acetal) (6i). Following the general procedure described above for the preparation of **6a**, from stannylcyclobutenone **5** (920 mg, 2.21 mmol, 1.06 equiv), 4-chlorocyclobutenone **3b** (363 mg, 2.10 mmol), $(PhCN)_2PdCl_2$ (8.0 mg, 0.021 mmol, 1 mol%), and tris(2-furyl)phosphine (10.0 mg, 0.043 mmol, 2 mol%) an orange oil was obtained. Purification by silica gel chromatography (hexane/EtOAc, 5/1) afforded 395 mg (72%) of **6i** as a white solid. The analytical sample was obtained by recrystallization (diisopropyl ether/hexane). Data for **6i**: mp 121.5–122.0 °C dec (diisopropyl ether/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 8.16 (exch s, 1H, OH), 7.09 (s, 1H, C(6)H), 4.26 (m, 4H, OCH_2CH_2O), 2.68 (t, J = 7.7, 2H, $C(5)CH_2$), 2.22 (s, 3H, $C(4)CH_3$), 1.57 (m, 2H, $CH_2CH_2CH_3$), 1.40 (hex, J = 7.2, 2H, CH_2CH_3), 0.94 (t, J = 7.2, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 192.23, 155.82, 154.85, 147.44, 133.78, 127.10, 119.00, 114.48, 66.39, 34.82, 32.00, 22.68, 13.89, 11.20; IR (CCl_4, cm^{-1}) 3374 (w) 2961 (m), 1760 (s), 1740 (m), 1607 (m), 1299 (m), 1252 (m), 1027 (s); TLC R_f 0.31 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{15}H_{18}O_4$ (MW 262.31): C, 68.69; H, 6.92. Found: C, 68.65; H, 6.96.

4-*n*-Butyl-3-hydroxy-5-methylbenzocyclobutenedione 1-(Ethylene acetal) (6j). Following the general procedure described above for the preparation of **6a**, from stannylcyclobutenone **5** (517 mg, 1.25 mmol, 1.04 equiv), 4-chlorocyclobutenone **3a** (206 mg, 1.19 mmol), $(PhCN)_2PdCl_2$ (4.0 mg, 0.010 mmol, 1 mol%), and tris(2-furyl)phosphine (5.0 mg, 0.021 mmol, 2 mol%) an orange oil was obtained. Purification by silica gel chromatography (hexane/EtOAc, 6/1) afforded 221 mg (71%) of **6j** as a white solid. The analytical sample was obtained by recrystallization (diisopropyl ether/hexane). Data for **6j**: mp 158–159 °C (diisopropyl ether/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) 7.87 (exch s, 1H, OH), 7.09 (s, 1H, C(6)H), 4.25 (m, 4H, OCH_2CH_2O), 2.66 (br t, J = 7.3, 2H, $C(4)CH_2$), 2.41 (s, 3H, $C(5)CH_3$), 1.42 (m, 4H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.2, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) 192.16, 155.83, 149.82, 147.13, 134.27, 132.45, 118.99, 115.81, 66.39, 30.84, 25.87, 22.96, 21.27, 13.89; IR (CCl_4, cm^{-1}) 3352 (br w), 2962 (m), 1758 (m), 1601 (m), 1308 (m), 1042 (m), 1024 (m); TLC R_f 0.40 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{15}H_{18}O_4$ (MW 262.31): C, 68.69; H, 6.92. Found: C, 68.64; H, 6.96.

4,6-Di-*n*-butyl-3-hydroxy-5-isopropoxybenzocyclobutenedione 1-(Ethylene acetal) (7a). Following the general procedure described above for the preparation of **6a** (reaction time 12 h),

from stannylcyclobutenone **5** (221 mg, 0.53 mmol, 1.0 equiv), 4-chlorocyclobutenone **4a** (145 mg, 0.53 mmol), $(PhCN)_2PdCl_2$ (4 mg, 0.01 mmol, 2 mol%), and tris(2-furyl)phosphine (5.0 mg, 0.021 mmol, 4 mol%) an orange oil was obtained. Purification by silica gel chromatography (hexane/EtOAc, 6/1) afforded 171 mg (89%) of **7a** as a colorless glass. Data for **7a**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.20 (exch s, 1H, OH), 4.24 (m, 5H, OCH_2CH_2O, $OCH(CH_3)_2$), 2.62 (m, 4H, C(4)CH_2, C(6)CH_2), 1.64–1.23 (m, 8H, $CH_2CH_2CH_3$, 2 sets), 1.31 (d, J = 6.1, 6H, $OCH(CH_3)_2$), 0.94 (m, 6H, CH_2CH_3, 2 sets); ^{13}C NMR (75.5 MHz, $CDCl_3$) 191.96, 163.58, 155.34, 147.43, 131.15, 128.95, 124.84, 118.70, 76.58, 66.40, 31.95, 30.93, 27.23, 24.84, 22.97, 22.91, 22.51, 13.88; IR (CCl_4, cm^{-1}) 3580 (br w), 2960 (m), 1755 (s), 1737 (s), 1298 (m), 1138 (m), 1104 (s), 1024 (m); TLC R_f 0.20 (hexane/EtOAc, 4/1); HRMS Calcd for $C_{21}H_{30}O_5$ (MW 362.47): 362.2093085. Found: 362.2093244.

3-Hydroxy-5-isopropoxy-4-methyl-6-phenylbenzocyclobutenedione 1-(Ethylene acetal) (7b) and 3-Hydroxy-5-isopropoxy-6-methyl-4-phenylbenzocyclobutenedione 1-(Ethylene acetal) (7c). Following the general procedure described above for the preparation of **6a** (reaction time 20 h), from stannylcyclobutenone **5** (351 mg, 0.85 mmol, 1.04 equiv), 4-chlorocyclobutenone **4b** (204 mg, 0.81 mmol), $(PhCN)_2PdCl_2$ (6.2 mg, 0.016 mmol, 2 mol%), and tris(2-furyl)phosphine (7.5 mg, 0.032 mmol, 4 mol%) an orange oil was obtained. The ^{1}H NMR of this crude material displayed two methyl groups at 2.24 and 2.27 ppm in a ratio of 2:1. Purification by silica gel chromatography (hexane/EtOAc, 6/1) afforded 158 mg (57%) of **7b/7c** as a colorless glass in a ratio of 2/1. Partial separation of the regioisomers could be achieved by silica gel chromatography (Et_2O/hexane, 1/1) to afford an upper band (R_f = 0.35, hexane/EtOAc, 2/1) (73 mg, 26%) identified as **7b**, and a mixture of upper and lower (R_f = 0.34, hexane/EtOAc, 2/1) bands (65 mg, 23%). The NMR data for **7c** were obtained from this mixed fraction. Data for **7b**: mp 175–179 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) 8.61 (br exch s, 1H, OH), 7.64 (m, 2H, *o*-Ph), 7.34 (m, 3H, *m,p*-Ph), 4.15 (m, 2H, OCH_aCH_aO), 3.92 (m, 3H, OCH_bCH_bO, $OCH(CH_3)_2$), 2.24 (s, 3H, C(4)CH_3), 1.02 (d, J = 6.1, 6H, $OCH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 191.58, 162.85, 156.79, 148.44, 135.12, 131.01, 129.17, 128.19, 127.48, 124.49, 123.48, 118.89, 76.13, 66.55, 22.08, 10.27; IR (CCl_4, cm^{-1}) 3550 (br w), 2980 (w), 1760 (m), 1607 (m), 1472 (w), 1450 (w), 1383 (w), 1372 (w), 1328 (w), 1302 (m), 1225 (w), 1173 (m), 1094 (m), 1024 (m); TLC R_f 0.35 (hexane/EtOAc, 2/1); HRMS Calcd for $C_{20}H_{20}O_5$ (MW 340.38): 340.1310739. Found: 340.1310740. Data for **7c**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.0 (br exch s, 1H, OH), 7.46–7.27 (m, 5H, Ph), 4.30 (m, 4H, OCH_2CH_2O), 3.77 (hept, J = 6.1, 1H, $OCH(CH_3)_2$), 2.27 (s, 3H, C(6)CH_3), 0.93 (d, J = 6.1, 6H, $OCH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 192.02, 163.17, 157.54, 146.70, 132.79, 130.58, 130.49, 128.55, 127.97, 126.94, 119.49, 118.53, 76.58, 66.60, 22.11, 12.16.

General Procedure for the Deprotection of 6 and 7: 3-Hydroxy-5-isopropoxy-4-methylbenzocyclobutenedione (18a). In a 50-mL round-bottomed flask fitted with a reflux condensor, a solution of ketal **6a** (350 mg, 1.32 mmol) in THF (20 mL) was treated with 6 N HCl (5 mL). The resulting solution was heated to reflux. After 30 min, the reaction mixture was cooled to room temperature and extracted with Et_2O (3 × 20 mL). The extracts were washed with brine (1 × 20 mL), combined, dried ($MgSO_4$), filtered through a pad of Celite, and concentrated to a yellow solid. Purification by silica gel chromatography (hexane/EtOAc, 4/1) and recrystallization (Et_2O/hexane) afforded 288 mg (99%) of **18a** as yellow plates. Data for **18a**: mp (Et_2O/hexane) 169–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.1 (exch s, 1H, O*H*), 7.00 (s, 1H, C(6)H), 4.74 (hept, J = 6.1, 1H, $CH(CH_3)_2$), 2.19 (s, 3H, C(4)CH_3), 1.44 (d, J = 6.0, 6H, $CH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) 193.74, 190.59, 170.87, 166.21, 153.99, 149.40, 123.68, 96.89, 72.93, 21.85, 9.62; IR (CCl_4, cm^{-1}) 3544 (br w), 2940 (w), 1770 (s), 1600 (m), 1480 (w), 1300 (w), 1220 (w), 1130 (m), 1110 (w); TLC R_f 0.30 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{12}H_{12}O_4$ (MW 220.23): C, 65.45; H, 5.49. Found: C, 65.51; H, 5.51.

5-*n*-Butyl-3-hydroxy-4-methylbenzocyclobutenedione (18i). Following the general procedure for **18a** above, from **6i** (297 mg, 1.13 mmol) a yellow solid was obtained. Purification by silica gel chromatography (hexane/EtOAc, 4/1) afforded 242 mg (98%) of **18i** as an amorphous yellow solid. Data for **18**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.1 (exch s, 1H, O*H*), 7.41 (s, 1H, C(6)H), 2.77 (t, J = 7.7, 2H, C(5)CH_2), 2.33 (s, 3H, C(4)CH_3), 1.65–1.40 (2 m, 4H, $CH_2CH_2CH_3$), 0.97 (t, J = 7.2, 3H, CH_2CH_3); ^{13}C NMR (7.5 MHz, $CDCl_3$) 193.15, 192.73, 168.67, 156.25, 155.31, 148.41, 132.09, 114.20, 34.66, 31.71, 22.57, 13.81, 11.96; IR (CCl_4, cm^{-1}) 3540 (br w), 2960 (m), 1770 (s), 1590 (m), 1250 (m), 1170 (w), 1120 (w); TLC R_f 0.48 (Et_2O/hexane, 2/1); HRMS calcd for $C_{13}H_{14}O_3$ (MW 218.25) 218.0942944, found 218.0942945.

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