Steric and Inductive Effects on the Hydrolysis of Quinone Bisketals

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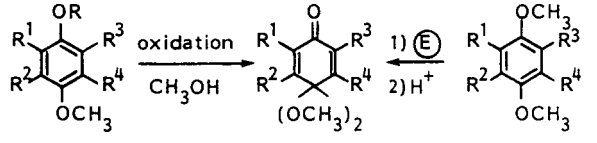
The effects of allylic substituents on the regiochemistry of monohydrolysis of tetralin-type quinone bisketals **12** have been studied. The requisite bisketals were prepared by anodic oxidation of the corresponding 1-substituted 5,8-dimethoxytetralin. Product studies establish that hydroxyl and ether functions at the allylic position preferentially afford quinone monoketals of type **13** wherein the ketal function nearest to the allylic substituent is hydrolyzed. The fluoro system also preferentially forms the monoketal **13** (R = F). A series of alkyl substituents were also studied, and increasing the size of the group led to increasing regioselectivity in favor of **13**. Only the $\Delta^{1,2}$-unsaturated systems **12j,k** preferentially gave monoketals in which the more distant ketal function had hydrolyzed. Kinetic studies established at least two major factors in the regiochemistry of the bisketal hydrolysis. While both the oxygenated and alkylated substituents gave monoketals **13** in which hydrolysis had selectively occurred at the nearer ketal function, the origins of the observed regioselectivity are different. Oxygenated systems gave the observed regiochemistry due to a rate retardation of the hydrolysis of the more distant ketal by what is proposed to be an inductive effect. However, alkyl substituents exerted their effect by increasing the rate of hydrolysis of the nearer ketal function due to a relief of strain energy.

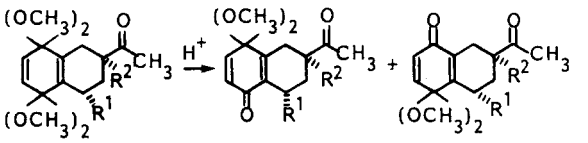
Quinone monoketals serve as valuable regiospecific quinone equivalents in organic synthesis.[1] In addition to the regiochemical control possible in Michael[1-4] type reactions with quinone monoketals, reactions of nucleophiles with monoketals may take a different course than the same reaction with a quinone. A recent review[1] has summarized the reactions of quinone monoketals, and the most recent applications have employed these moieties in the synthesis of anthracyclinones,[3] indoles,[4] and isoindoles.[5]

The most generally useful routes to the quinone monoketal are the chemical[6] [thallium(III) salts[7] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[8]] or electrochemical oxidation of *p*-methoxyphenols,[9a] the electrochemical oxidation of trimethylsilyl ethers of *p*-methoxyphenols,[9b] and



1, R = H or $(CH_3)_3Si$ 2 3

the anodic oxidation of methoxylated aromatics followed by mild acid hydrolysis.[10] All of these routes are subject to regiochemical constraints since the former two require the appropriate *p*-methoxyphenol and the latter route is dependent on the regiochemistry of hydrolysis of the quinone bisketal. In fact, quinone bisketals unsymmetrically substituted adjacent to the ketal linkage often selectively produce one quinone monoketal[10b] upon hydrolysis. However, bisketals such as **4a** show virtually no regioselectivity in their monohydrolysis.

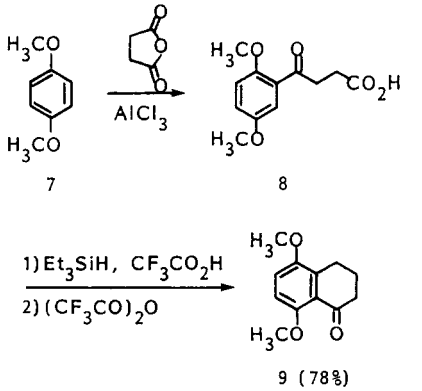


4a, $R^1 = R^2 = H$	5a	1:1	6a
b, $R^1 = OCH_3$, $R^2 = OSi(t\text{-}Bu)(CH_3)_2$	5b	~90:10	6b

An interesting mechanistic problem was presented by the discovery that an allylic oxygen functionality[3a,c,d] afforded regiochemical control in the hydrolysis of the bisketal **4b**. This was a key feature of our regioselective synthesis of anthracyclinones,[3a] and an understanding of the factors responsible for the regiochemical control would be of general interest. Studies reported herein establish the effect of a variety of allylic substituents on the regiochemistry of bisketal hydrolysis in a tetralin-type system and provide a reasonable, mechanistic rationale for the effect. The results of these studies should be valuable in designing regioselective routes to other quinone monoketals.

Synthesis of the Model Systems for Study

The 1,4-dimethoxytetralin ring system was selected to study the effect of allylic substituents on the regiochemistry of bisketal hydrolysis. The ketone **9** was readily available via the reaction sequence outlined in eq 1. The



7 8 9 (78%) (1)

(1) Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74. Fugita, S. *Yuki Gosei Kagaku Kyokaishi* **1981**, 307.
(2) Parker, K. A.; Kang, S. *J. Org. Chem.* **1980**, *45*, 1218.
(3) (a) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. W. *Tetrahedron* **1984**, *40*, 4625. (b) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 932. (c) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263. (d) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318. (e) Keay, B. A.; Rodrigo, R. *Tetrahedron* **1984**, *40*, 4597. (f) Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1980**, 932.
(4) Coates, R. M.; MacManus, P. A. *J. Org. Chem.* **1982**, *47*, 4823.
(5) Parker, K. A.; Cohen, I. D. *Tetrahedron Lett.* **1984**, *25*, 4917.
(6) For complete referencing on the chemical oxidation of aromatics to quinone monoketals, see ref 1 and 10.
(7) McKillop, A.; Perry, D. H.; Edwards, D. H.; Antus, S.; Darkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282.
(8) Büchi, G.; Chu, P.; Hoppmann, A.; Mak, C.; Pearce, A. *J. Org. Chem.* **1978**, *43*, 3983.
(9) (a) Nilsson, A.; Rontan, A.; Parker, V. *Tetrahedron Lett.* **1975**, 1107. Foster, C. H.; Payne, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 2834. (b) Steward, R. F.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4999.
(10) (a) Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369. (b) Henton, D. R.; Anderson, D. K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422.

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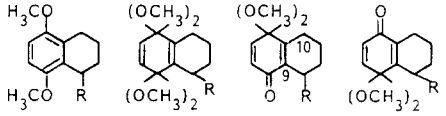
Table I. Anodic Oxidation/Hydrolysis Studies of 10a–k

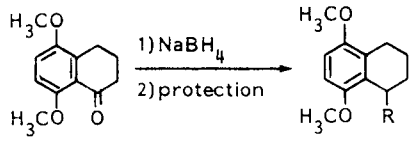


10 12 13 14

entry	R	yield of 12,[a] %	yield of 13/14[a] %	ratio[b] of 13/14	
				−20 °C	+22 °C
1	**a**, OH	97	92	8.4:1	8:1
2	**b**, OCH_3	98	93	6.2:1	6:1
3	**c**, $OSi(t\text{-}Bu)(CH_3)_2$	92	90	3.3:1	2.9:1
4	**d**, OCH_2OCH_3	98	91	3.5:1	
5	**e**, CH_3	95	98	1.5:1	1.5:1
6	**f**, CH_3CH_2	90	96	3:1	
7	**g**, *i*-Pr	99		6.5:1	
8	**h**, *t*-Bu	97	98	10.5:1	7:1
9	**i**, F	76	92	10.5:1	11:1
10	**j**, see text	88	88	1:5	1:5
11	**k**, see text	96	91	1:10	1:8

[a] Yield of crude product(s) showing no major impurities by ^1H NMR. [b] Ratio determined by ^1H NMR spectroscopy.

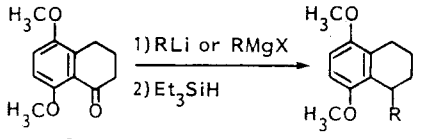
direct conversion of **8** to **9** was especially convenient since the crude product from the triethylsilane reduction[11] was directly cyclized to the tetralone **9**.[12] Reduction of **9** with sodium borohydride and functionalization afforded the oxygenated derivatives **10a–d** used in the anodic oxidation/hydrolysis studies.



9 10

a, R = $OH[OSi(CH_3)_3]$; b, R = OCH_3;
c, R = $OSi(t\text{-}Bu)(CH_3)_2$; d, R = OCH_2OCH_3

A second series of compounds employed in the study were designed to assess the importance of steric effects on the bisketal hydrolysis. These systems were prepared by addition of organolithium reagents or Grignard reagents to the ketone **9** followed by triethylsilane reduction. Not surprisingly, enolization was a major complication in the reaction of **9** with isopropyl and *tert*-butyl organometallic derivatives. This synthetic work was completed before

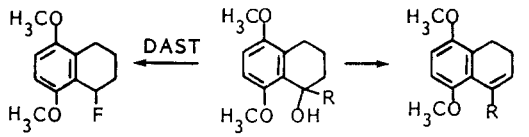


9 10

e, R = CH_3; f, R = C_2H_5; g, R = $i\text{-}C_3H_7$;
h, R = *t*-Bu

the report that cerium(III) chloride promoted the addition reaction of organometallics to carbonyl groups subject to enolization;[13] however, it was of interest to investigate this point in the reaction of *tert*-butyllithium with **9**. Indeed, the overall yields of **10h** from the reaction of **9** and *tert*-butyllithium in the absence and presence of cerium(III) chloride were 13% and 42%, respectively. Any future work involving addition of organometallic reagents to **9** could markedly benefit from the use of cerium(III) chloride.

The final compounds employed in the studies were the fluoro system **10i** and the unsaturated systems **10j,k** prepared as shown in eq 2. The benzylic fluoro system **10i** was especially labile, and the anodic oxidation chemistry of **10i** (vide infra) was performed immediately after its preparation.



(2)

10i 10a, R = H 10j, R = H
10ℓ, R = CH_3 10k, R = CH_3

Anodic Oxidation/Hydrolysis Studies

The results from the anodic oxidation and subsequent hydrolyses of the resulting bisketals from the tetralins **10a–k** are given in Table I. All anodic oxidations were conducted in 2% methanolic potassium hydroxide in a single cell (except **10j,k**, for which a divided cell was employed) at constant current. Standard workup afforded the crude bisketals which were used directly for the hydrolysis studies. The specific details and spectroscopic data for the bisketals are given in the Experimental Section and supplementary material, and only pertinent points are noted here. As stated earlier, the benzylic fluoride **10i** was extremely labile and was not purified prior to anodic oxidation, so bisketal **12i** was recrystallized prior to hydrolysis. For **10a** (R = OH) the unprotected hydroxyl group complicated the product mixture in the anodic oxidation: thus, the oxidation was conducted on the trimethylsilyl derivative, with the protecting group being removed during the workup of the reaction mixture, to afford **12a**.

The preparative hydrolyses were conducted in acetone/5% aqueous acetic acid (4:1) at −20 °C for 24–48 h, and the reaction mixtures were neutralized with saturated sodium bicarbonate. As is apparent from the temperature-dependence data listed in Table II, the regioselectivity of the monohydrolysis is only slightly improved at −20 °C relative to 22 °C. For the systems having oxygenated substituents (entries 1–4), the major monoketals **13a–c** and

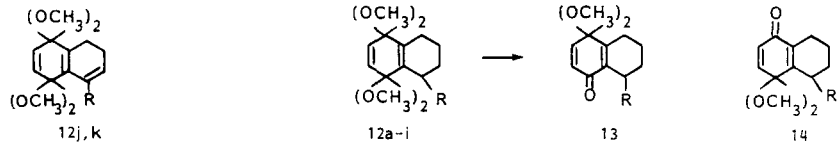
(11) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2673. Swenton, J. S.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4188.

(12) The keto acid **8** was previously converted to **9** by Wolff–Kishner reduction or hydrogenation followed by polyphosphoric acid cyclization in about 45–50% overall yield.[13] The yield from **7** to **9** in this work was 78%.

(13) Moore, J. A.; Rahm, R. *J. Org. Chem.* **1961**, *26*, 1109. Shimizu, T.; Horaguchi, T.; Watanabe, A. *Bull. Chem. Soc. Jpn.* **1979**, *46*, 1772.

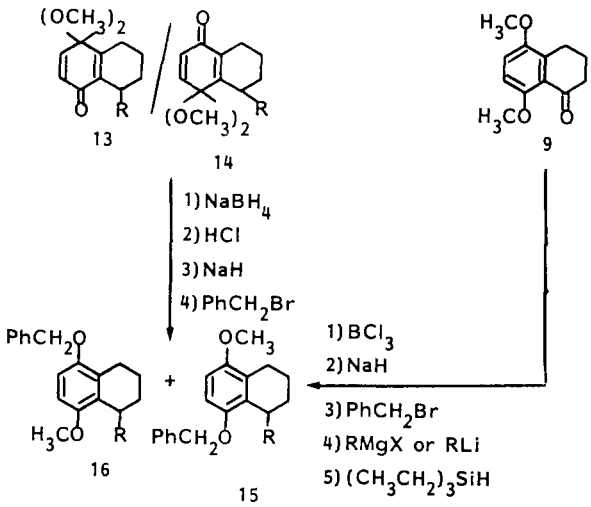
(14) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

Table II. Kinetics of Biketal Hydrolysis at 22 °C



entry	compd	R	10^4k, s^{-1}	10^4k, s^{-1}	10^4k, s^{-1}
1	**11**	H	5.8	2.9	2.9
2	**12a**	OH	2.2	2.0	0.2
3	**12b**	OCH_3	3.5	3.0	0.5
4	**12c**	$OSi(t\text{-}Bu)(CH_3)_2$	2.7	2.0	0.8
5	**12e**	CH_3	7.5	4.5	3.0
6	**12h**	*t*-Bu	15.1	13.0	1.9
7	**12i**	F	0.75	0.68	0.06
8	**12j**	H	3.8	0.63	3.2
9	**12k**	CH_3	2.2	0.24	1.8

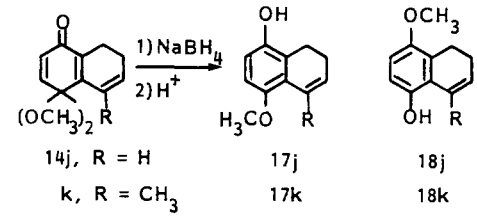
Scheme I. General Procedure for Assignment of Structure for Monoketals



the minor monoketals **14a,d** were isolated pure.[15] Systems that yielded difficult-to-separate mixtures were first reduced to the respective phenols, which were separated either directly or as derivatives. The structures for the phenols or phenol derivatives were established by spectroscopic analysis or by comparison with authentic samples prepared via conventional synthetic methods. A detailed discussion is given in the supplementary material. The ratios of the monoketals from hydrolysis of **12a–d** were readily determined by integration of the tertiary allylic hydrogen in the ^1H NMR spectrum: for monoketals of structure **13**, the position for this proton was about δ 0.1 lower than for this proton in **14**.

For entries 5–8, the regioisomeric monoketals were much more difficult to separate chromatographically, and only the major monoketals **13g,h** were obtained pure. For the remaining compounds, the mixtures of monoketals were reduced with sodium borohydride to afford the corresponding phenols. The phenols were separated chromatographically and benzylated. Comparison of major benzylated aromatic compound **15** with an authentic sample prepared by standard chemical methods established the regiochemistry of the major monoketal. The general scheme for the structure proofs is given in Scheme I, and the details are supplied in the supplementary material. The ratios of monoketals were obtained by integration of the appropriate resonances in the ^1H NMR spectra.

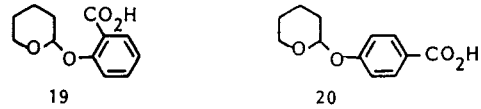
The final compounds studied were the fluoro system **12c** and the triene compounds **12j,k**. The major monoketal from hydrolysis of **12i** was assigned as **13i** by virtue of the magnitude of the ^{19}F coupling to the carbons in the ^{13}C NMR spectrum. For this monoketal, the ^{19}F coupling constant at C-10 (δ 157.5) was 6 Hz while that at C-9 (δ 133.0) was 16 Hz. This assignment is fully supported by data given in the supplementary material. The ratio of the two monoketals **13i** and **14i** was determined by integration of the resonances in the ^{19}F NMR spectra. For the vinyl systems, **14j** and **14k** were isolated pure and reduced to **17j,k**. Phenols **17j,k** showed similar, but different,



spectroscopic properties (IR, NMR) than phenols **18j,k** which were independently prepared. The ratio of monoketals in this latter case was determined by integration of the methoxyl region of the ^1H NMR spectrum of the hydrolysis mixture.

Discussion

The mechanism of acetal/ketal hydrolysis has been extensively studied, and it is generally accepted that the rate-determining step involves formation of a carbonium ion with either specific hydronium ion or general acid catalysis.[16] Several possibilities were considered for the regiocontrol exerted by allylic substituents on the hydrolysis of the quinone bisketals discussed above.[17] Intramolecular general acid catalysis of an acetal or ketal linkage can result in rate accelerations as high as 10^4–10^6 in selected systems,[18] **19** and **20**. A rate change of only



a fraction of the above value could account for the observed regiochemistry if the allylic oxygen function were facilitating the hydrolysis of the adjacent bisketal. Such a possibility would involve protonation of the more basic

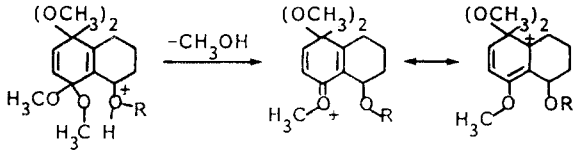
(15) While the *tert*-butyldimethylsiloxyl group does not afford the highest regioselectivity in the monohydrolysis of a quinone bisketal, it was employed in our anthracyclicone synthesis[3a] because it gave the most reproducible yields in subsequent synthetic steps.

(16) (a) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581. (b) Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264.

(17) For a thorough discussion of stereoelectronic effects in the hydrolysis of bisketals, see ref 10b.

(18) Fife, T. H.; Anderson, E. *J. Am. Chem. Soc.* **1971**, *93*, 6610.

ether oxygen ($pK_a \sim -4$) vs. the ketal oxygen ($pK_a \sim -5$), followed by intramolecular proton transfer and loss of methanol to afford **22**.



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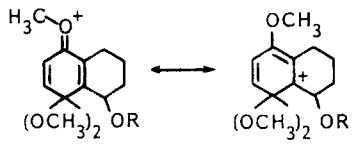
Second, the inductive effect of the allylic substituent could retard the rate of ionization to form cation **23** relative to cation **22**. This type of rationale is essentially that used in explaining the predominant meta substitution in the electrophilic reactions of protonated or trialkylated anilines.[19] Furthermore, the slower rate of hydrolysis (~10)[20]



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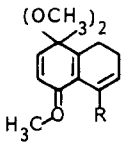
of benzoquinone bisketal relative to 2,2-dimethoxypropane could be ascribed to a rate-retarding inductive effect of the second ketal function on the hydrolysis of the first ketal.

Finally, a rate acceleration from relief of steric interactions could account for selective hydrolysis of the ketal moiety adjacent to the allylic substituent. Both rate accelerations[21] and retardations[22] have been attributed to steric effects in acetal/ketal hydrolysis. Such an explanation would be especially attractive in understanding the high regioselectivity observed in the *tert*-butyl system **12h**.

Simple kinetic studies of the bisketal hydrolyses would rule out some of the above-mentioned possibilities. Intramolecular catalysis by a hydroxyl group or steric acceleration would lead to an overall rate enhancement, while an inductive effect would result in a rate retardation. The rates for hydrolysis of bisketals **11** and **12a–c,e,h–k** were measured at 22 °C in a mixture of tetrahydrofuran, water, and acetic acid. The data showed excellent linearity through three to four half-lives when treated as a pseudo-first-order reaction. The results of these determinations are collected in Table II. Since the ratio of monoketals is time invariant, the individual rate constants for hydrolysis of each ketal of the bisketal can be determined from the overall rate and the product ratio. While these numbers are subject to more error than the measured rates since the ratios of the isomeric monoketals are probably not better than ±10%, the numbers are useful for this discussion.

The data of Table II establish that the regioselectivity observed in the hydrolysis of the oxygenated and fluoro systems (entries 2–4, 7) is not due to an acceleration in the rate of **13** formation but to a retardation in the rate of **14** formation. This effect is greatest for the most electronegative substituent fluorine, which slows down the rates for formation of **13i** and **14i** by factors of ~3 and ~50, respectively. Thus, the effect of an allylic electronegative substituent on the regiochemistry of the bisketal hydrolysis is reasonably attributed to the inductive effect discussed above. In contrast to the above systems, the rates for formation of **13e,h** are accelerated by factors of ~2 and ~4.5, respectively. Such a result is reasonably interpreted as a steric acceleration of the bisketal ionization. The results from bisketals **12j,k** are interesting since the regiochemical outcome is a reversal of the previous compounds. This change in regiochemistry is primarily due to the slower rate of formation of monoketals **13j,k** vs. that of **14j,k**. Furthermore, methyl substitution has a small retarding effect on the rates of hydrolysis of both ketal functions in **12k**. An attractive idea for explaining the slower rates for formation of **13j,k** is that steric interaction of the allylic substituent with the *p*-methoxyl group raises the transition-state energy of the reaction.



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Conclusions[23]

Electron-withdrawing substituents change the regiochemistry of the hydrolysis of quinone bisketals primarily by retarding the rate of hydrolysis of the more distant ketal. This result can be rationalized by assuming that the electron-withdrawing group deactivates the hydrolysis of the more distant ketal by inductively destabilizing the dispersal of positive charge in the allylic cation system. Such an inductive destabilization in the transition state for the other ketal center is less effective. In the case of alkyl groups, hydrolysis is accelerated for the ketal nearer to the alkyl group, and the selectivity of the hydrolysis increases with the size of the alkyl group. Rate studies establish that the alkyl groups result in a rate acceleration for hydrolysis of the nearer ketal. This would reasonably be attributed to some relief of steric strain in the transition state for ionization. Finally, while conjugation of a double bond with the quinone bisketal leads to good regioselectivity, the exact nature of the effect remains to be established.

Experimental Section[24]

5,8-Dimethoxytetralone (9). To a vigorously stirred 25 °C solution of **8** (11.2 g, 0.047 mmol) in CF_3CO_2H (25 mL) was added

(19) See, for example: Hine, J. "Physical Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1962; pp 374–376.

(20) Chaturvedi, R. K.; Adams, J.; Cordes, E. H. *J. Org. Chem.* **1968**, *33*, 1652.

(21) Anderson, E.; Fife, T. H. *J. Am. Chem. Soc.* **1971**, *93*, 1701. Kreevoy, M. M.; Morgan, C. R.; Taft, R. W. *J. Am. Chem. Soc.* **1960**, *82*, 3064.

(22) Fife, T. H.; Hagopian, L. *J. Org. Chem.* **1966**, *31*, 1722.

(23) The free-energy differences between the hydrolysis of the two ketal functions in all of the systems studied are small. However, an 80:15 vs. a 50:50 mixture of isomeric monoketals can have important synthetic consequences.

(24) The following abbreviations have been used throughout the text: PE (low boiling petroleum ether); THF (tetrahydrofuran). All anodic oxidations were essentially conducted as described in ref 10a. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Measurements with standard samples indicate that the reported melting points are probably 1–2 °C lower than the correct value. IR spectra were taken on a Perkin-Elmer Model 282B grating spectrometer in the indicated phase: only strong absorptions are reported. ^1H NMR and ^{13}C NMR spectra were recorded at 80 and 20.1 MHz, respectively, in $CDCl_3$ as solvent. The reported chemical shifts for the AB quartets are calculated. Apparent multiplicities are reported, and in some cases, signals reported as triplets are in fact closely spaced doublet of doublets. Mass spectra and exact mass measurements were obtained by C. Weisenberger on a Kratos MS-30 mass spectrometer connected to a DS-55 data system. The kinetic measurements were made on a Beckman DU-7 equipped with the kinetics package. Tetrahydrofuran was freshly distilled from benzophenone/sodium prior to use. All other anhydrous solvents used for reactions were freshly dried and distilled. All reactions were performed under a nitrogen atmosphere. Combustion analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Aluminum and silica gel were from E. Merck and Co., and flash silica gel was obtained from EM reagents (230–400 mesh). "Workup as usual" consisted of extraction of the product (CH_2Cl_2 or Et_2O), drying over $CaSO_4$ or Na_2SO_4, and concentration in vacuo, followed by drying under oil pump vacuum.

dropwise triethylsilane (20.5 mL, 0.13 mol). After being stirred for 10 min, the reaction mixture was concentrated in vacuo, and the dark brown oil was taken up in 10% KOH (50 mL) and Et_2O (50 mL). The phases were separated, the aqueous phase was acidified (concentrated HCl), and the acid was extracted with CH_2Cl_2 (3 × 40 mL) and worked up as usual to afford 10.3 g (98%) of the acid as an oil suitable for use in the next step. Recrystallization of a portion of this material from Et_2O gave a light yellow solid, mp 66–67 °C (lit.[13] mp 64–65 °C).

To the acid from above in CF_3CO_2H (30 mL) was added $(CF_3CO_2)_2O$ (30 mL, 0.21 mol), and after 5 min the reaction mixture was concentrated in vacuo. The reaction mixture was partitioned in a mixture of CH_2Cl_2 (50 mL) and 10% KOH, and the product was extracted with additional CH_2Cl_2 to afford after workup a dark brown oil. Flash chromatography on silica gel (5:1 CH_2Cl_2/Et_2O as eluant) afforded **9** (7.6 g, 78% overall), mp 60–62 °C (lit.[13] mp 58–62 °C).

10a (R = Trimethylsiloxy). The reaction of **10a** (R = OH, 614.7 mg, 2.96 mmol), chlorotrimethylsilane (1.69 mL, 13.3 mmol), and $[(CH_3)_3Si]_2NH$ (2.8 mL, 13.2 mmol) in pyridine (7.7 mL) was allowed to proceed at 50 °C for 24 h. The reaction was quenched with saturated sodium bicarbonate solution (20 mL) and worked up as usual to yield a light brown oil. Flash chromatography (1:1 hexane/CH_2Cl_2) yielded **10a** (R = trimethylsiloxy) as a colorless oil (762.7 mg, 92%): IR (neat) 2940, 1480, 1465, 1440, 1360, 1350, 1100, 1080, 1030, 1010, 960, 890, 840 cm^{-1}; ^1H NMR δ 6.66 (br s, 2 H), 5.17–5.03 (m, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.80–1.40 (m, 6 H), 0.16 (s, 9 H); ^{13}C NMR δ 152.0 (s), 151.6 (s), 128.3 (s), 127.9 (s), 109.0 (d), 107.2 (d), 62.0 (q), 55.7 (q), 55.1 (q), 31.7 (t), 23.2 (t), 15.9 (t), 0.56 (3 C, q); mass spectrum, exact mass calcd for $C_{15}H_{24}O_3Si$ m/e 280.1495, obsd m/e 280.1548.

10b. To a slurry of 60% sodium hydride mineral oil dispersion (30 mg, 1.1 mmol, washed with hexane) in THF (15 mL) was added **10a** (R = OH, 100 mg, 0.481 mmol). The mixture was heated to reflux for 2 h and cooled to 40 °C, methyl iodide (0.15 mL, 1.17 mmol) was added, and the mixture was allowed to stir at 40 °C for 6 h and then at room temperature overnight. The reaction mixture was diluted with water (10 mL), concentrated in vacuo, and then extracted with EtOAc (2 × 50 mL). Workup and flash chromatography (CH_2Cl_2) yielded **10b** as a light yellow oil (86.4 mg, 81%): IR (neat) 2920, 2830, 1480, 1460 (sh), 1440 (sh), 1350, 1080 cm^{-1}; ^1H NMR δ 6.67 (s, 2 H), 4.69–4.47 (m, 1 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.43 (s, 3 H), 3.1–1.44 (m, 6 H); mass spectrum, exact mass calcd for $C_{13}H_{18}O_3$ m/e 222.1256, obsd m/e 222.1267.

10c. The reaction of **10a** (R = OH, 0.1 g, 0.48 mmol) and dimethyl *tert*-butylsilyl chloride (128 mg, 4.81 mmol) in DMF (10 mL), with imidazole (128 mg) as base at 50 °C, was allowed to proceed for 6 h. The reaction was quenched with saturated sodium bicarbonate (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with water (4 × 100 mL), dried, and concentrated in vacuo to yield **10c** as a brown oil. Flash chromatography (1:1 hexane/CH_2Cl_2) gave a white crystalline solid (148 mg, 0.460 mmol, 95%): mp 61.2–62 °C; IR (KBr) 2940, 2860, 1560, 1530 (sh), 1480, 1260, 1250, 1100, 1080, 1030, 1010, 960, 880, 830, 770, 710 cm^{-1}; ^1H NMR δ 6.65 (br s, 2 H), 5.10–4.95 (m, 1 H), 3.77 (s, 6 H), 2.8–1.0 (m, 6 H), 0.86 (s, 9 H), 0.15 (s, 3 H); mass spectrum, exact mass calcd for $C_{18}H_{30}O_3$ m/e 322.1964, obsd m/e 322.1988.

10d. A solution of **10a** (R = OH, 100 mg, 0.48 mmol), CH_2Cl_2 (10 mL), diisopropyl ethyl amine (2 mL, 5.21 mmol, 10.7 equiv per OH), and chloromethyl methyl ether (0.4 mL, 4.81 mmol, 10 equiv per OH) was heated to reflux (orange color developed) for 10 h. The mixture was cooled to room temperature, 5% aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was worked up as usual to afford **10d** as a light orange oil. Flash chromatography (CH_2Cl_2) yielded a colorless oil (110.9 mg, 91%): IR (neat) 2930, 1475, 1460 (sh), 1440, 1250, 1140, 1090, 1030, 705 cm^{-1}; ^1H NMR δ 6.66 (s, 2H), 4.95 (AB q, J = 6.4 Hz, 1 H), 4.92 (br s, 1 H), 4.70 (AB q, J = 6.4 Hz, 1 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.41 (s, 3 H), 2.92–1.25 (m, 6 H); mass spectrum, exact mass calcd for $C_{14}H_{20}O_4$ m/e 252.1362, obsd m/e 252.1373.

10e. To **9** (835.8 mg, 4.058 mmol) dissolved in THF (15 mL) and cooled to −70 °C was added 1.5 M CH_3Li in Et_2O (2.9 mL), and the reaction mixture was stirred for 0.5 h. The reaction was quenched with water (2 mL), and the mixture was concentrated in vacuo and then extracted with CH_2Cl_2 (3 × 30 mL). Workup as usual afforded a yellow oil. Flash chromatography (CH_2Cl_2 as eluant) gave the pure alcohol (855.5 mg, 93%). Recrystallization from PE/CH_2Cl_2 gave colorless crystals: mp 58.2–59.5 °C (lit.[25] mp 71 °C); IR (KBr) 3530 (br), 2970, 1480–1430, 1360, 1330, 1270, 1250, 1075, 1050 cm^{-1}; ^1H NMR δ 6.67 (s, 2 H), 4.63 (s, 1 H), 3.86 (s, 3 H), 3.75 (s, 3 H), 2.7–2.0 (m, 2 H), 2.0–1.5 (m, 4 H), 1.58 (s, 3 H); ^{13}C NMR δ 151.3 (2 C), 132.0, 126.8, 108.1, 107.7, 71.1, 55.2 (2 C), 38.3, 28.9, 23.7, 19.6; mass spectrum, exact mass calcd for $C_{13}H_{18}O_3$ m/e 222.1256, obsd m/e 222.1284.

To a mixture of the above alcohol (761.1 mg, 3.36 mmol) and Et_3SiH (2.5 mL, 15.7 mmol) was added CF_3CO_2H (5 mL), and the light yellow reaction mixture was then concentrated in vacuo to give a light yellow oil. Flash chromatography (15:2 and then 3:1 PE/CH_2Cl_2) gave **10e** (617.3 mg, 89%) as a colorless oil:[25] IR (film) 2920, 1470, 1430 (sh), 1245, 1090, 1070 cm^{-1}; ^1H NMR δ 6.61 (s, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.3–2.0 (m, 3 H), 2.0–1.5 (m, 4 H), 1.19 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 151.4 (2 C), 132.3, 126.5, 106.8, 106.4, 55.1 (2 C), 29.4, 26.7, 23.3, 20.6, 17.0; mass spectrum, exact mass calcd for $C_{13}H_{18}O_2$ m/e 206.1387, obsd m/e 206.1335.

10f. To a solution of **9** (0.698 g, 3.39 mmol) in dry THF at −70 °C was added EtMgBr (1.2 mL, 2 M THF solution, 1.05 equiv), and the solution was stirred for 1 h. After addition of water (2 mL), the reaction mixture was concentrated in vacuo, and the organic material was extracted with CH_2Cl_2 (3 × 30 mL) and worked up as usual to afford a light yellow oil. Flash chromatography (CH_2Cl_2) gave the alcohol [452.1 mg, 57% (84% based on uncovered starting material)] and recovered starting material (227.1 mg). The pure liquid showed the following IR (film) 3600–3500, 2980, 1480, 1465 (sh), 1440, 1390, 1335, 1250, 1090, 1065, 980, 950 cm^{-1}; ^1H NMR δ 6.66 (s, 2 H), 4.31 (s, 1 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 2.8–1.2 (m, 8 H), 0.89 (t, J = 6.4 Hz, 3 H); ^{13}C NMR δ 151.4, 151.3, 132.5, 127.3, 108.1, 107.7, 73.4, 55.2 (2 C), 32.9, 32.1, 23.8, 18.9, 7.5; mass spectrum, exact mass calcd for $C_{14}H_{20}O_3$ m/e 236.1413, obsd m/e 236.1391.

A mixture of the above alcohol (446.3 mg, 1.80 mmol) and Et_3SiH (2 mL, 12.6 mmol) was reacted with CF_3CO_2H (3 mL) as for **10e**. Workup followed by flash chromatography (15:1 and then 3:1 PE/CH_2Cl_2) gave **10f** (401.4 mg, 96%) as a colorless liquid: IR (film) 2940, 1480, 1465 (sh), 1400, 1250, 1100, 1080 cm^{-1}; ^1H NMR δ 6.61 (s, 2 H), 3.77 (s, 6 H), 3.00–1.00 (m, 9 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 151.4 (2 C), 132.4, 126.7, 106.9, 106.5, 55.3, 33.6, 26.7, 24.3, 23.2, 17.0, 12.4; mass spectrum, exact mass calcd for $C_{14}H_{20}O_2$ m/e 220.1463, obsd m/e 220.1429.

10g. Reaction of **9** (847.5 mg, 4.11 mmol) in THF (15 mL) at −70 °C with a solution of 2 M *i*-PrMgCl (2.16 mL, 1.05 equiv) in THF followed by workup and flash chromatography (1:1 PE/CH_2Cl_2) gave starting **10a** (244.1 mg) and the product alcohol (137.6 mg, 42% yield): IR (film) 3600–3360, 2940, 1470, 1435, 1390, 1335, 1250, 1185, 1160 cm^{-1}; ^1H NMR δ 6.66 (s, 2 H), 3.98 (s, 1 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 3.1–1.32 (m, 7 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.53 (d, J = 6.9 Hz, 3 H); mass spectrum, exact mass calcd for $C_{15}H_{22}O_3$ m/e 250.1569, obsd m/e 250.1549.

Reduction of the above alcohol (244.1 mg, 0.97 mmol) with Et_3SiH (1.15 mL, 7.2 mmol) in CF_3CO_2H (2.5 mL) gave after workup and flash chromatography (15:1 and then 3:1 PE/CH_2Cl_2) **10g** (197.4 mg, 86%) as an oil: IR (neat) 2940, 1475, 1460 (sh), 1440, 1250, 1090 cm^{-1}; ^1H NMR δ 6.62 (s, 2 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.15–1.40 (m, 8 H), 0.86 (d, J = 6 Hz, 6 H); mass spectrum, exact mass calcd for $C_{15}H_{22}O_2$ m/e 234.1619, obsd m/e 234.1610.

10h. A reaction flask containing cerium chloride heptahydrate (2.48 g, 6.7 mmol) was heated at 140 °C (0.03 mm) for 2 h and then cooled under a nitrogen atmosphere to −78 °C. THF (10 mL) was added to the flask followed by *tert*-butyllithium (4.75 mL of a 1.2 M hexane solution). Then **9** (1.38 g, 6.7 mmol) in THF (10 mL) was added, and the solution was stirred for 40 min at −78 °C. Addition of saturated NH_4Cl and standard workup followed by flash chromatography on silica gel (CH_2Cl_2 as eluant) gave **10h** (0.7 g, 42%). Additional product was present in overlapping fractions, which could be obtained pure by further chromatography. Recrystallization from PE/CH_2Cl_2 gave the

(25) Coillard, J.; Mentzer, C. *Bull. Soc. Chim.* **1953**, *20*, 168.
(26) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

analytical sample: mp 120–121 °C; IR (KBr) 3485, 2950, 1475, 1460 (sh), 1455, 1440, 1375, 1335, 1250, 1097, 1065, 950, 805 cm^{-1}; ^1H NMR δ 6.68 (s, 2 H), 5.38 (br s, 1 H), 3.77 (s, 6 H), 2.9–1.3 (m, 6 H), 0.88 (s, 9 H); ^{13}C NMR δ 152.4, 151.4, 131.0, 129.4, 108.5, 108.3, 78.9, 55.8, 55.3, 41.6, 35.8, 26.4 (3 C), 23.4, 20.1. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.65; H, 9.17.

Reduction of the alcohol (157.2 mg, 0.595 mmol) with Et_3SiH (0.35 mL, 2.2 mmol) in CF_3CO_2H (5 mL) followed by flash chromatography on silica gel (first with hexane and then with 1:1 hexane/CH_2Cl_2) gave **10h** (139.2 mg, 94%): IR (neat) 2940, 1475, 1440, 1250, 1092, 1070 cm^{-1}; ^1H NMR δ 6.61 (s, 2 H), 3.25 (s, 3 H), 3.20 (s, 3 H), 3.3–1.0 (m, 7 H), 0.86 (s, 9 H); ^{13}C NMR δ 152.1, 151.1, 130.3 (2 C), 107.4, 107.0, 55.8, 55.1, 39.2, 36.9, 29.0 (3 C), 24.2, 21.6, 20.2; mass spectrum, exact mass calcd for $C_{16}H_{24}O_2$ m/e 248.1777, obsd m/e 248.1790.

10k. A solution of CH_3Li (2.5 mL of a 1.2 M solution in Et_2O, 1.2 equiv) in THF (20 mL) was cooled to −78 °C. Then a solution of **9** [0.521 g, 2.53 mmol in THF (10 mL)] was added over a period of 10 min. The mixture was stirred for 0.5 h, the reaction was quenched by adding 20% HCl (10 mL), and the mixture was concentrated in vacuo. Extraction of the residue with CH_2Cl_2 (3 × 30 mL) and workup as usual afforded a light yellow oil. Flash column chromatography (1:1 CH_2Cl_2/PE as eluant) gave colorless oil **10k** (465 mg, 90%): IR (film) 2930, 2830, 1480, 1465, 1435, 1225, 1135, 1090, 1055 cm^{-1}; ^1H NMR δ 6.72 (s, 2 H), 6.5–6.2 (m, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 2.68–2.45 (m, 2 H), 2.40–1.76 (m, 5 H); mass spectrum, exact mass calcd for $C_{13}H_{16}O_2$ m/e 204.1150, obsd m/e 204.1139.

13a and 14a. Anodic oxidation (45 min, 0.8 A) of **10a** (206.3 mg, 0.74 mmol) in 2% CH_3OH/KOH (75 mL) at −20 °C followed by workup gave **12a** as a crude light yellow oil (194.8 mg, 97%), which was used directly in the next step: IR (neat) 3600–3200 (br), 2940, 2830, 1460, 1440, 1400, 1295, 1205, 1170, 1145 (br), 980, 960 cm^{-1}; ^1H NMR δ 6.21 (AB q, J = 8 Hz, 1 H), 6.13 (AB q, J = 8 Hz, 1 H), 4.62–4.36 (m, 1 H), 3.46 (br s, 1 H), 3.37 (s, 3 H), 3.16 (s, 3 H), 3.13 (s, 3 H), 3.10 (s, 3 H), 2.5–1.2 (m, 6 H).

To the crude **12a** (194.8 mg, 0.721 mmol) in $(CH_3)_2CO$ (15 mL) at −20 °C was added 5% HOAc (5 mL), and the solution was stored for 48 h. Workup gave a mixture of **13a** and **14a** as a light brown oil (150.1 mg, 0.67 mmol, 92%). Flash chromatography (2:1 hexane/CH_2Cl_2) yielded **13a** (129 mg, 80%): IR (neat) 3650–3200 (br), 2940, 2830, 1675, 1645, 1610, 1405, 1295, 1100–1060 (br) cm^{-1}; ^1H NMR (CCl_4) δ 6.78 (AB q, J = 10 Hz, 1 H), 6.41 (AB q, J = 10 Hz, 1 H), 4.81–4.58 (m, 1 H), 3.21 (s, 3 H), 3.20 (br s, 1 H), 2.45–1.20 (m, 6 H); ^{13}C NMR δ 185.9 (s), 154.6 (s), 144.1 (d), 137.3 (s), 132.0 (d), 83.9 (s), 62.4 (d), 50.9 (q), 50.8 (q), 29.7 (t), 23.5 (t), 17.4 (t); mass spectrum, exact mass calcd for $C_{12}H_{16}O_4$ m/e 224.1048, obsd m/e 224.1080.

The second monoketal **14a** (15.3 mg, 9%) showed the following: IR (neat) 3600–3200 (br), 2940, 2820, 1675, 1650, 1625, 1290, 1160 (br), 990, 960 cm^{-1}; ^1H NMR δ 6.78 (AB, q, J = 10 Hz, 1 H), 6.38 (AB q, J = 10 Hz, 1 H), 4.68–4.52 (m, 1 H), 3.43–3.17 (br, 1 H), 3.40 (s, 3 H), 3.17 (s, 3 H), 2.76–1.32 (m, 6 H); ^{13}C NMR δ 194.4 (s), 147.0 (s), 141.4 (s), 137.8 (s), 131.7 (d), 97.2 (s), 62.3 (d), 51.1 (q), 51.0 (q), 29.5 (t), 22.4 (t), 16.3 (t); mass spectrum, exact mass calcd for $C_{12}H_{16}O_4$ m/e 224.1048, obsd m/e 224.1077.

13b and 14b. Anodic oxidation (0.7 h, 0.8 A) of **10b** (201 mg, 0.901 mmol) in 2% CH_3OH/KOH (75 mL) at −5 °C followed by workup gave the bisketal **12b** (0.252 g, 0.88 mmol) as a crude brown oil (0.25 g, 98%): IR (neat) 2940, 2830, 1410, 1395, 1290, 1205, 1190, 1175, 1140, 1075 (br), 1010, 940 cm^{-1}; ^1H NMR δ 6.12 (s, 2 H), 4.02–3.78 (m, 1 H), 3.36 (s, 3 H), 3.24, 3.22, 3.18 (s, 12 H), 3.15, 2.5–1.0 (m, 6 H).

This material was dissolved in $(CH_3)_2CO$ (15 mL) and cooled to −20 °C, 5% HOAc (5 mL) was added, and the solution was stored for 48 h. Workup gave a mixture of two monoketals in the ratio 6.2:1 as determined by integration of the methine signals at δ 4.27–4.23 and 4.04–3.98 in the ^1H NMR spectrum. Flash chromatography (CH_2Cl_2) gave pure **13b** (142.9 mg, 65%): IR (neat) 2950, 2820, 1670, 1640, 1620, 1450, 1400, 1350, 1290, 1205, 1190, 1085, 1055, 1010, 960, 840 cm^{-1}; ^1H NMR δ 6.72 (AB q, J = 10 Hz, 1 H), 6.42 (AB q, J = 10 Hz, 1 H), 4.37–4.17 (m, 1 H), 3.41 (s, 3 H), 3.19 (s, 6 H), 2.50–1.10 (m, 6 H); ^{13}C NMR δ 183.7 (s), 154.3 (s), 142.9 (d), 136.0 (s), 132.5 (d), 95.0 (s), 68.3 (d), 51.3 (q), 50.9 (q), 50.7 (q), 25.7 (t), 23.1 (t), 15.7 (t); mass spectrum, exact mass calcd for $C_{13}H_{18}O_4$ m/e 238.1205, obsd m/e 238.1166.

The minor isomer was not obtained pure.

13c and 14c. Anodic oxidation (1.5 h, 1 A) of **10c** (206.5 mg, 0.641 mmol) in 2% CH_3OH/KOH (75 mL) at −5 °C followed by workup as usual gave crude **12c** as a light brown oil (228.67 mg, 0.65 mmol, 92%), which was used directly in the next step: IR (neat) 2930, 2850, 2825, 1460, 1250, 1205, 1175, 1140, 1075 (br), 1020, 1000, 950, 870, 830, 770 cm^{-1}; crude ^1H NMR δ 6.10 (br s, 2 H), 5.63–5.41 (m, 1 H), 3.21 (s, 3 H), 3.16 (s, 3 H), 3.13 (s, 6 H), 2.5–1.0 (m, 6 H), 0.88 (s, 9 H), 0.10 (s, 6 H).

To the crude **12c** (220.4 mg, 0.573 mmol) in acetone (15 mL) at −20 °C was added 5% HOAc (5 mL), and the hydrolysis was allowed to proceed for 60 h. Workup gave the monoketals **13c** and **14c** as a crude brown oil (174.6 mg, 0.51 mmol). Integration of the methine hydrogens in the ^1H NMR spectrum at δ 4.82–4.75 and 4.66–4.60 showed the **13c**/**14c** ratio to be 3.3:1. This mixture of monoketals was reduced, and the reduction products were characterized as described in the supplementary material.

13d and 14d. Anodic oxidation (40 min, 1 A) of **10d** (203.9 mg, 0.804 mmol) in 2% CH_3OH/KOH (75 mL) at −5 °C followed by workup gave **12d** as a light brown oil (0.252 g, 98%), which was used directly in the next step: IR (neat) 2940, 2820, 1460, 1440, 1390, 1380, 1305, 1250, 1240, 1050 (br), 960 cm^{-1}; ^1H NMR δ 6.12 (s, 2 H), 4.89 (AB q, J = 7 Hz, 1 H), 4.59 (AB q, J = 7 Hz, 1 H), 4.38–4.18 (m, 1 H), 3.38 (s, 3 H), 3.18 (s, 3 H), 3.17 (s, 3 H), 3.15 (s, 3 H), 3.14 (s, 3 H), 2.35–1.00 (m, 6 H).

To the crude product **12d** (154.1 mg, 0.491 mmol) in acetone (15 mL) at −20 °C was added a 5% solution of HOAc (5 mL), and hydrolysis was allowed to proceed for 48 h. Standard workup gave the mixture of monoketals **13d** and **14d** as a brown oil (120 mg, 0.44 mmol, 91%). Integration of the methine hydrogen signals at δ 4.68–4.58 and 4.48–4.43 showed the ratio of monoketals **13d**/**14d** to be 3.5:1.0. Flash chromatography (2:1 PE/CH_2Cl_2) yielded a pure sample of the two monoketals in addition to overlapping fractions. The major isomer **13d** (41.0 mg, 31%) showed the following: IR (neat) 2940, 1680, 1650, 1625, 1295, 1210, 1150, 1100, 1060, 1035, 965 cm^{-1}; ^1H NMR δ 6.71 (AB q, J = 10 Hz, 1 H), 6.41 (AB q, J = 10 Hz, 1 H), 4.90 (AB q, J = 6 Hz, 1 H), 4.61 (partially obscured, 1 H), 4.60 (AB q, J = 6 Hz, 1 H), 3.43 (s, 3 H), 3.24 (s, 3 H), 3.20 (s, 3 H), 2.60–1.60 (m, 6 H); mass spectrum, exact mass calcd for $C_{14}H_{20}O_5$ m/e 268.1311, obsd m/e 268.1296.

The minor monoketal, **14d**, showed the following: mp 68–69 °C; IR (KBr) 2940, 1680, 1650, 1290, 1150, 1100, 1080, 1065, 1037 cm^{-1}; ^1H NMR δ 6.71 (AB q, J_{AB} = 10 Hz, 1 H), 6.40 (AB q, J_{AB} = 10 Hz, 1 H), 4.92 (AB q, J_{AB} = 7 Hz, 1 H), 4.64 (AB q, J_{AB} = 7 Hz, 1 H), 4.58–4.30 (m, 1 H), 3.42 (s, 3 H), 3.24 (s, 3 H), 3.20 (s, 3 H), 2.06–1.06 (m, 6 H); exact mass calcd for $C_{14}H_{20}O_5$ m/e 268.1311, obsd m/e 268.1296.

13e and 14e. Anodic oxidation (40 min, 0.8 A) of **10e** (604.1 mg, 2.93 mmol) in 2% CH_3OH/KOH (75 mL) at 0 °C was continued until no starting material could be detected by TLC. The resulting solution was concentrated in vacuo and extracted with CH_2Cl_2 (3 × 30 mL). Workup as usual gave **12e** (760.5 mg, 95%) as a clear oil: IR (film) 2930, 1450, 1280, 1200, 1060 (br), 1040, 940 cm^{-1}; ^1H NMR δ 6.11 (s, 2 H), 3.19, 3.17, 3.13 (3 s, 12 H), 2.80–1.35 (m, 7 H), 1.19 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 139.6, 136.4, 132.4, 131.2, 95.9, 94.9, 49.9 (q, 4 C), 30.3 (t), 26.0 (d), 21.4 (t), 19.9 (q), 16.3 (t).

A solution of **12e** (415.8 mg, 1.55 mmol) in $(CH_3)_2CO$ (20 mL) was cooled to −20 °C, and cold 5% HOAc (5 mL) was added. After 48 h at −20 °C the reaction was quenched with saturated $NaHCO_3$ (20 mL), and the reaction was worked up as usual to give a light yellow oil. The crude ^1H NMR spectrum showed **13e** and **14e** in the ratio 1.5:1 [integration of the methyl resonances at δ 1.24 (d, J = 6.74 Hz, 3 H) and 1.08 (d, J = 7.2 Hz, 3 H)]. The chemical transformations and separations of the products from this mixture are described in the supplementary material.

13f and 14f. Anodic oxidation (40 min, 0.8 A) of **10f** (383.5 mg, 1.74 mmol) in 2% CH_3OH/KOH (75 mL) at 0 °C was continued until the absorption for starting material (λ_{max} 289 nm) decreased to within 5% of its initial value. Concentration in vacuo and workup as usual afforded the crude bisketal **12f** as a light yellow oil (441.3, 90%), which was used directly in the next step: IR (film) 2940, 2830, 1300, 1150, 1070 (br), 955 cm^{-1}; ^1H NMR 6.11 (s, 2 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 3.14 (s, 3 H), 3.11 (s, 3 H), 2.80–1.10 (m, 9 H), 0.87 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 140.0,

136.5, 132.6, 131.4, 96.2, 95.3, 50.4, 50.2, 50.1 (2 C), 33.0, 24.2, 21.2, 16.0, 11.9.

A solution of **12f** (441.3 mg, 1.56 mmol) in $(CH_3)_2CO$ (20 mL) was cooled to −20 °C, and cold 5% HOAc (5 mL) was added. After 2 days at −20 °C, saturated $NaHCO_3$ (30 mL) was added, and the mixture was worked up to afford a yellow oil (392 mg, 96%). Integration of the olefinic region of the ^1H NMR spectrum gave a 3:1 mixture of regioisomeric monoketals. This was in qualitative agreement with the ratio of peak heights in the ^{13}C NMR spectrum. The supplementary material describes the chemical transformations and separation of the pure products from this mixture of monoketals.

13g and 14g. The anodic oxidation (40 min, 0.25 A) of **10g** (191.9 mg, 082 mmol) in 2% CH_3OH/KOH (75 mL) at 0 °C gave **12g** (280.2 mg, 99%), which was used directly in the next step: IR (film) 2940, 2830, 1465, 1390, 1305, 1245, 1230, 1070 (br), 960 cm^{-1}; ^1H NMR δ 6.20 (AB q, J = 10 Hz, 1 H), 6.04 (AB q, J = 10 Hz, 1 H), 3.24 (s, 3 H), 3.15 (s, 3 H), 3.11 (s, 3 H), 3.09 (s, 3 H), 2.80–1.25 (m, 8 H), 0.93 (d, J = 7 Hz, 3 H), 0.82 (d, J = 7 Hz, 3 H).

The monohydrolysis with $(CH_3)_2CO$ (20 mL) and 5% HOAc (5 mL)) of **12g** (240.2 mg, 0.81 mmol) at −20 °C was allowed to proceed for 48 h. Workup gave a light yellow oil (141 mg, 66%). The ^1H NMR spectrum of the crude reaction mixture showed **13g** and **14g** in the ratio 6.5:1 from intergration of the olefinic region. Flash chromatography (1:1 PE/CH_2Cl_2) yielded **13g** and **14g** in addition to overlapping fractions and quinone. Spectroscopic data for **13g** showed the following: IR (film) 2930, 1670, 1640, 1620, 1460, 1370, 1290, 1210, 1100, 1060, 960, 840 cm^{-1}; ^1H NMR δ 6.62 (AB q, J = 10 Hz, 1 H), 6.36 (AB q, J = 10 Hz, 1 H), 3.17 (s, 3 H), 3.11 (s, 3 H), 3.00–1.30 (m, 8 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.76 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 184.8, 162.1, 142.8, 140.6, 132.9, 95.5, 50.9, 50.8, 36.6, 30.0, 23.0 (2 C), 21.1, 18.9, 18.7; mass spectrum, exact mass calcd for $C_{15}H_{22}O_3$ m/e 250.1497, obsd m/e 250.1526.

The minor isomer was not obtained pure.

13h and 14h. Electrolysis (0.5 h, 0.7 A) of **10h** (234.3 mg, 0.95 mmol) in 2% CH_3OH/KOH (70 mL) at 0 °C was followed by UV until disappearance of λ_{max} 291-nm absorption. Workup gave **12h** (289.9 mg, 97% crude) as a light yellow oil suitable for use in the next step: IR (neat) 2940, 2820, 1460, 1390, 1200, 1090, 1070 (br), 960 cm^{-1}; ^1H NMR δ 6.33 (AB q, J = 10 Hz, 1 H), 5.99 (AB q, J = 10 Hz, 1 H), 3.34 (s, 3 H), 3.15 (s, 3 H), 3.12 (s, 3 H), 3.02 (s, 3 H), 2.5–1.0 (m, 7 H), 1.04 (s, 9 H); ^{13}C NMR δ 142.4, 137.7, 133.1, 130.8, 96.4, 95.0, 50.8, 50.7, 50.3, 49.0, 40.3, 34.7, 31.2 (3 C), 27.2, 20.0, 17.3.

To the crude **12h** (289.9 mg, 0.93 mmol) in $(CH_3)_2CO$ (15 mL) at −20 °C was added 5% aqueous HOAc (5 mL), and the solution was stored for 48 h. The crude ^1H NMR spectrum showed a 10.5:1 mixture of monoketals (250 mg, 96%) as determined by integration of the *tert*-butyl resonances at δ 1.05 and 1.37. Flash chromatography (1:1 PE/CH_2Cl_2) gave **13h** (147.6 mg, 57%): IR (neat) 2950, 1675, 1640, 1365, 1290, 1280, 1150, 1100, 1070 (br), 965, 840 cm^{-1}; ^1H NMR δ 6.65 (AB q, J = 10 Hz, 1 H), 6.43 (AB q, J = 10 Hz, 1 H), 3.26 (s, 3 H), 3.11 (3 H), 2.5–1.0 (m, 6 H), 0.87 (s, 9 H); ^{13}C NMR δ 185.2, 153.6, 142.3, 140.1, 132.7, 95.5, 51.0, 50.7, 38.1, 36.0, 29.3 (3 C), 23.6, 21.9, 19.8; mass spectrum, exact mass calcd for $C_{16}H_{24}O_5$ m/e 264.1725, obsd m/e 264.1718.

The minor isomer could not be obtained pure, but its reduction product was characterized as described in the supplementary material.

10i, 13i, and 14i. A solution of **10a** (R = OH, 0.665 g, 3.20 mmol) in CH_2Cl_2 (10 mL) was added slowly to a −78 °C solution of diethylaminosulfur trifluoride (0.7 mL, 5.7 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was warmed to room temperature, and water was added. The product was extremely labile, affording the elimination product and hydrogen fluoride on standing. Workup in the usual manner gave a yellow oil, which showed the following: IR (neat) 2930, 2830, 1600, 1480, 1460 (sh), 1440, 1340, 1310, 1300, 1090, 1060 cm^{-1}; ^1H NMR δ 6.68–6.80 (m, 2 H), 5.4 (br d, J_{HF} = 49 Hz, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.20–1.05 (m, 6 H); ^{13}C NMR δ 129.0, 128.8, 110.8 (J_{HF} = 4 Hz), 109.9, 107.9 (J_{HF} = 2 Hz), 106.4, 86.4 (J_{HF} = 164 Hz), 56.0, 55.6, 28.9 (J_{HF} = 22 Hz), 22.9, 16.2.

This product was immediately dissolved in 2% KOH/CH_3OH (50 mL) and electrolyzed at 0 °C (0.5 A, 45 min) to afford **12i** after workup as a light yellow oil, which was crystallized from PE/CH_2Cl_2 [76%; first crop (547.6 mg), second crop (93.4 mg), third crop (18.7 mg)]: mp 52–54.5 °C; IR (KBr) 2940, 2830, 1205, 1180, 1070 (br), 960 cm^{-1}; ^1H NMR δ 6.24 (br s, 2 H), 5.30 (br d, J_{HF} = 48 Hz, 1 H), 3.22 (s, 3 H), 3.20 (s, 6 H), 3.16 (s, 3 H), 2.45–1.20 (m, 6 H); ^{13}C NMR δ 144.2, 143.9 (J_{HF} = 10 Hz), 132.7, 131.7 128.2 (J_{HF} = 22 Hz), 95.0, 81.1 (J_{HF} = 164 Hz), 51.3, 50.7 (2 C), 50.5 (2 C), 28.8 (J_{HF} = 20 Hz), 21.9 (J_{HF} = 4 Hz), 15.6; mass spectrum, exact mass calcd for $C_{14}H_{21}O_4F$ m/e 272.1423, obsd m/e 272.1457.

To a solution of **12i** (547.6 mg, 2.0 mmol) in $(CH_3)_2C{=}O$ (15 mL) at −20 °C was added 5% HOAc (5 mL), and the reaction mixture was stored for 48 h. Workup gave a mixture of two monoketals as a light yellow oil. Flash chromatography (neutral aluminum oxide, Activity III, CH_2Cl_2) did not afford a separation but yielded from integration of the ^{19}F NMR signals [two triplets with extensive additional coupling, $J \sim 40$ Hz at δ −158.4 (**13j**) and −151.2 (**14j**)] a 10.5:1 mixture of **13i** and **14i** as a clear oil (393.7 mg, 1.75 mmol, 88%). The spectroscopic data for **13i** were obtained from the above mixture: IR (film, neat) 2940, 1680, 1650, 1635, 1405, 1290, 1210, 1100, 1040, 960, 905 cm^{-1}; ^1H NMR δ 6.77 (AB q, J = 10 Hz, 1 H), 6.46 (AB q, J = 10 Hz, 1 H), 5.65 (d of m, J_{HF} = 46 Hz, 1 H), 3.21 (s, 6 H), 2.73–1.05 (m, 6 H); ^{13}C NMR δ 183.0, 157.50 (J_{CF} = 6 Hz), 143.1, 133.1 (J_{CF} = 16 Hz), 132.1, 94.8, 79.9 (J_{CF} = 166 Hz), 51.0, 50.9, 28.1 (J_{CF} = 22 Hz), 23.1 (J_{CF} = 2 Hz), 15.7; mass spectrum, exact mass calcd for $C_{12}H_{15}O_3F$ m/e 226.1005, obsd m/e 226.1015.

13j and 14j. Anodic oxidation (40 min, 0.2 A) of **10j** (0.198 g, 1.04 mmol) in 75 mL of 1% KOH/CH_3OH at 0 °C was continued until TLC showed no remaining starting material. Workup as usual afforded the bisketal **12j** as a light brown oil (0.21 g, 80%), which was used directly in the next step: IR (film, neat) 2940, 2820, 1460, 1390, 1300, 1285, 1205, 1150, 1070 (br), 960 cm^{-1}; ^1H NMR δ 6.3–5.8 (m, 4 H), 3.20 (s, 12 H), 2.23 (br s, 4 H).

To a solution of **12j** (210 mg, 0.83 mmol) in $(CH_3)_2C{=}O$ (20 mL) at −20 °C was added 5% HOAc (0.5 mL), and the reaction mixture was stored for 48 h. Workup gave a mixture of two monoketals as a brown oil. Integration of the methoxy region (δ 3.20 and 3.25) showed the **14j**/**13j** ratio to be 5:1. Flash chromatography (3:1 CH_2Cl_2/PE) gave pure **14j**: IR (film, neat) 2940, 2830, 1670, 1640, 1630, 1460, 1440, 1390, 1300, 1280, 1210, 1150, 1070 (br), 950 cm^{-1}; ^1H NMR δ 6.61 (J_{AB} = 10 Hz, 1 H), 6.35 (J_{AB} = 10 Hz overlapping with a broad singlet at δ 6.28, total area 3 H), 3.20 (s, 6 H), 2.8–2.0 (br m, 4 H); ^{13}C NMR δ 184.6 (s), 145.2 (s), 141.8 (d), 135.7 (d), 132.3 (d), 131.3 (s), 122.2 (d), 94.7 (s), 51.0 (2 C, q), 22.4 (t), 17.7 (t); mass spectrum, exact mass calcd for $C_{12}H_{14}O_3$ m/e 206.0943, obsd m/e 206.0948.

The minor monoketal was not obtained pure.

13k and 14k. The anodic oxidation (2 h, 0.15 A) of **10k** (425 mg, 2.08 mmol) in 2% CH_3OH/KOH (75 mL) at 0 °C (divided cell) gave **12k** (590 mg, 96%), which was used directly in the next step: IR (film) 2940, 2860, 1205, 1100, 1065 (br), 950 cm^{-1}; ^1H NMR δ 6.08 (s, 2 H), 5.8–5.65 (m, 1 H), 3.23 (s, 3 H), 3.20 (s, 3 H), 2.4–1.7 (m, 7 H).

The monohydrolysis [$(CH_3)_2CO$ (20 mL) and 5% HOAc (5 mL)] of **12k** (590 mg, 1.99 mmol) at −20 °C was allowed to proceed for 48 h. Workup gave the mixture of monoketals as a light yellow oil (400 mg, 91%). The ^1H NMR spectrum of the crude reaction mixture showed **13k** and **14k** in the ratio 1:8.5 from integration of the methoxy region. Flash column chromatography (CH_2Cl_2 as eluant) gave **14k** (220 mg, 50%) and a mixture of **13k** and **14k** (170 mg, 39%). Spectroscopic data for **14k** showed the following: IR (film) 2940, 1670, 1630, 1300, 1100, 1060 (br) cm^{-1}; ^1H NMR δ 6.55 (AB q, J = 10 Hz, 1 H), 6.39 (AB q, J = 10 Hz, 1 H), 6.2–5.9 (m, 1 H), 3.20 (s, 6 H), 2.6–1.7 (m, 7 H); ^{13}C NMR δ 184.9, 145.6, 143.3, 133.9, 133.1, 132.5, 131.2, 96.4, 50.7 (2 C), 22.4, 20.1, 18.9; mass spectrum, exact mass calcd for $C_{13}H_{16}O_3$ m/e 220.1093, obsd m/e 220.1096.

General Procedure for Kinetics of Bisketal Hydrolysis. To a 22 °C solution of 0.25 mL of 1.71 M aqueous acetic acid (pH 2.2) in a UV cell in the thermostated chamber of a Beckman DU-7 ultraviolet spectrometer was added 1.5 mL of a 22 °C solution of the bisketal in THF, giving a resulting solution of pH 4.2. The final concentration of bisketal was (3.8–17.1) × 10^{-4} M, and the rate constants were within experimental error when the initial concentration of bisketal was changed by a factor of 3 (compound **12b**). The rates were monitored by observing the increase in

optical density at the appropriate wavelengths, usually 315 and 295 nm. The rate constants were determined from the slope of a plot of log A/A_o vs. time by using the infinity optical density for the value of A_o. The plots showed excellent linearity up to three to four half-lives. Representative data are given in the supplementary material. The rate constants were readily reproducible within ±5% and should be accurate within ±10%.

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Supplementary Material Available: Experimental details of the structure proofs for compounds **13b,c,e-k** and **14b,c,e-h** and representative kinetic plots of the data (14 pages). Ordering information is given on any current masthead page.

Fluorination of Aromatic Derivatives with Fluoroxytrifluoromethane and Bis(fluoroxy)difluoromethane

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Fluoroxytrifluoromethane (CF_3OF) and bis(fluoroxy)difluoromethane $CF_2(OF)_2$ are formed by the reaction of F_2 with CO and CO_2, respectively, over a CsF catalyst in a continuous-stream process. Both reagents react with aromatic substrates by an electrophilic substitution mechanism to yield fluoro-substituted derivatives. Fluorobenzene is produced in good yield from benzene, and aniline derivatives afford monofluorination products. Acetanilide (**1**), *N*-phenylmethanesulfonamide (**2**), α,α,α-trifluoroacetanilide (**3**), and 1,1,1-trifluoro(*N*-phenyl)methanesulfonamide (**4**) react with either reagent to yield mixtures of *o*- and *p*-fluoro-substituted derivatives. Solvent effects and competitive rate experiments demonstrate a preference for ortho substitution, especially in aprotic, nonpolar solvents. With particular substrates, these fluorinating agents are of practical synthetic utility, e.g., 2-fluoro-4-(trifluoromethyl)aniline is produced in high yield by fluorinating the intermediate 4-(trifluoromethyl)acetanilide (**6**) with CF_3OF. Activated substrates such as toluene, xylenes, anisole, and cresols give mixtures of products which reduce the synthetic utility of these reagents. Nitrobenzene is fairly unreactive toward CF_3OF and gives low yields of substitution products.

The selective introduction of fluorine on an aromatic ring is not an easy synthetic task, and interest remains high in this type of process because fluoro-substituted aromatic derivatives show promise in a variety of applications, from agricultural chemicals to pharmaceuticals.

The Schiemann reaction, in which a diazonium, tetrafluoroborate is decomposed, converts an aniline to a fluorobenzene derivative, is the prominent method.[1] However, the reaction conditions, variable yields, and troublesome byproducts make this reaction a poor selection for any large scale industrial process.

Chloro- or bromo-substituted aromatic compounds bearing electron-withdrawing groups react under vigorous conditions with fluoride ion by nucleophilic displacement to yield fluoro derivatives. The positional requirement for electron-withdrawing substitutents limits the synthetic utility of this type of reaction.

Chlorination and bromination by a variety of reagents are usually accomplished by electrophilic substitution reactions. However, there are few fluorinating agents that introduce fluorine on an aromatic ring under selective and controlled conditions. Reactions with elemental fluorine afford unselective polyfluorination of the ring because of fluorine's extreme reactivity. The reactivity of fluorine can be quantitatively related to other halogens.[2] Reactions conducted at high dilution and extremely low conversion levels yield a Hammett-type correlation where $\rho^+ = -2.45$ when δ^+ values were used. This compares to typical values for chlorination ($\rho^+ = -6$ to -9) and bromination ($\rho^+ = -13$) which show fluorination to have a very low activation energy in electrophilic aromatic substitution reactions. Although isolated reports have appeared which claim selective fluorination with F_2,[3] there is, as yet, no optimum synthetic method.

In the design of an acceptable fluorinating agent, the strategy has been adopted of first treating elemental fluorine with another reagent to make it less reactive in subsequent reactions. There are a number of examples in this category. Xenon difluoride, XeF_2, does fluorinate both activated and deactivated substituted aromatic rings in moderate and varying yields.[4] Elemental fluorine reacts with sodium acetate to yield acetyl hypofluorite, CH_3CO-OF, which exhibits reactions that lead to monofluorination of activated aromatic rings.[5] Cesium fluoroxysulfate[6] and silver difluoride[7] have also been demonstrated to be reagents that yield selective monofluorination of aromatic substrates.

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