The Unusually Slow Hydrolysis Rate of Silyl Methyl Ketals in Benzoquinone Systems. The Question of Siloxy Stabilization of an Adjacent Positive Charge and Stereoelectronic Effects on Ketal Hydrolysis

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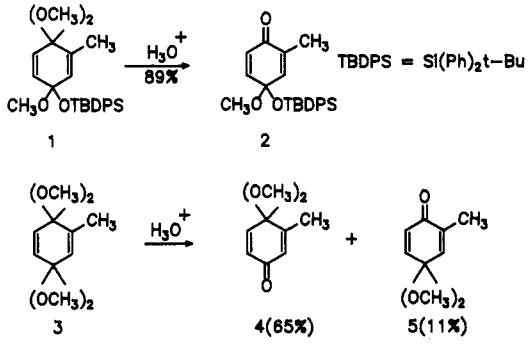
The kinetics of the acid-catalyzed monohydrolysis of six quinone bisketals were studied under pseudo-first-order conditions. The *tert*-butyldimethylsilyl methyl and the *tert*-butyldiphenylsilyl methyl ketals respectively hydrolyze about 400 times slower than does the corresponding dimethyl ketal and react nearly at the rate of the ethylene glycol ketal. An important consideration in understanding these results was the carbonium ion stabilizing ability of the siloxy substituent. Thus, σ and σ^+ values for the *tert*-butyldimethylsiloxy and the *tert*-butyldiphenylsiloxy groups were measured. These values indicated that siloxy groups are nearly as effective as a methoxy group in stabilizing a positive center provided a low-energy conformer is available for interaction of the oxygen nonbonding electron pair with the π-center. If delocalization of the oxygen lone-pair electrons by the silicon is important, it does not manifest itself in the σ or σ^+ values. The data collected also illustrate the strong conformational dependence of siloxy groups interacting with π-systems, and it is this effect that is thought to be the major contributor to the lower rate of hydrolysis observed for the silyl methyl ketal moieties in these quinone systems.

Introduction

Quinone monoketals are useful synthetic intermediates often best prepared from 1,4-dialkoxy aromatics via the two-step sequence, anodic oxidation/acid hydrolysis.[1] We recently reported that the silyl alkyl ketal analogue of these compounds (i.e., **2**) further extends the chemistry of these quinone equivalents since the latent carbonyl can be generated under basic conditions by using tetrabutylammonium fluoride.[2] Interestingly, the regiochemical outcome of the monohydrolysis of **1** is opposite that observed for **3** and a number of other alkyl-substituted quinone bisketals.[3] This not only serves as a method for preparing quinone monoketals that are regiochemical equivalents to those obtained from hydrolysis of the tetramethyl quinone bisketals but also presents an interesting mechanistic question. We report herein the kinetics of the monohydrolysis of several quinone bisketals having the dimethyl, ethylene, and silyl methyl linkages and studies directed at understanding the origin of the slower hydrolysis rate of the silyl methyl ketal moiety in these compounds.

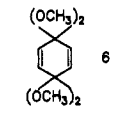
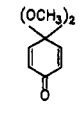
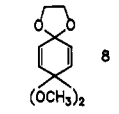
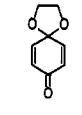
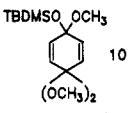
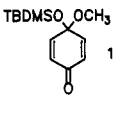
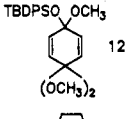
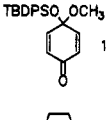
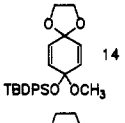
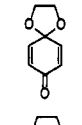
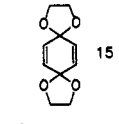
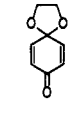


Kinetic Studies

Although the product percentages cited for **1** and **3** suggested a slower rate of acid hydrolysis of the silyl methyl linkage relative to a dimethyl ketal, kinetic studies were conducted to establish the magnitude of this rate reduction. Bisketals of entries 1–4 and 6 (Table I) were readily obtained via anodic oxidation of the appropriate aromatic substrate. However, the starting material for preparation of the bisketal **14** (entry 5) was not available. Since preliminary studies indicated that the silyl methyl ketal hydrolyzes more slowly than do dimethyl ketals and since quinone bisketals are known to undergo ketal exchange reactions,[4] the expedient approach to **14** was an exchange reaction of dimethyl bisketal **12**. Indeed, reaction of **12** with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid afforded **14** (73%).

Table I shows the relative rates obtained from the pseudo-first-order monohydrolyses of six quinone bisketals determined in a 2.5 M solution of aqueous acetic acid/

Table I. Relative Rates of Hydrolysis of Quinone Bisketals at 25 °C

entry	bisketal	monoketal	rel rate[a]
1	 6	 7	616[b]
2	 8	 9	596
3	 10	 11	284
4	 12	 13	244
5	 14	 9	1.6
6	 15	 9	1.0[b]

[a] Average of duplicate or triplicate measurements of the pseudo-first-order rate constants. [b] Rate divided by 2 to correct for the statistical factor.

(1) For reviews and leading references, see: Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74. Swenton, J. S. *Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley: New York, 1988; Vol. II, p 899.

(2) Stern, A.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 2763.

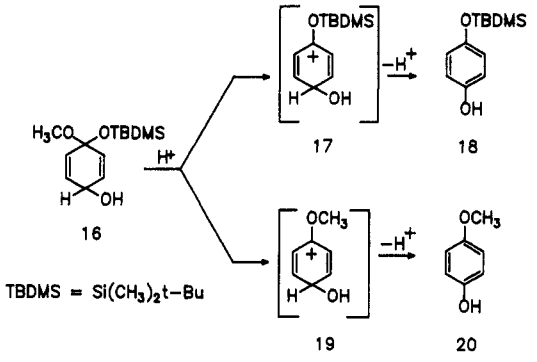
(3) Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422.

(4) Capparelli, M. P.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 5360.

0022-3263/89/1954-2953$01.50/0

tetrahydrofuran (1:2.1) at 25 °C. These data establish the magnitude of the slower rate of acid hydrolysis of the silyl methyl ketal versus the dimethyl ketal in the benzoquinone bisketal series. They also indicate that the nature of the unhydrolyzed ketal does not appreciably affect the rate of ketal hydrolysis. Thus, comparing entries 3 and 4 to entry 1 indicates that replacing a dimethyl ketal with a silyl methyl ketal retards the hydrolysis of the remaining (dimethyl) ketal by a factor of only ≈2.5. Comparison of entry 3 with entry 4 establishes that the inductive effects from the substituents on silicon (*tert*-butyldimethyl vs *tert*-butyldiphenyl) do not appreciably affect the rate of the hydrolysis.

Electron-Donating Character and Basicity of Siloxy Groups. Ascertaining which group—methoxy or siloxy—first leaves in the ketal hydrolysis is important in understanding the observed rate retardation. We know of no method to answer this question for the silyl methyl ketals of interest herein. However, this question can be answered for a closely related system. Reduction of the silyl methyl quinone monoketal **11** with sodium borohydride in ethanol afforded the labile alcohol **16**. Reacting this alcohol with a catalytic amount of acid would generate a carbonium ion at the carbon analogous to that formed in the ketal hydrolysis. Loss of a proton from this cation would then generate a stable hydroquinone monoether: *p*-(*tert*-butyldimethylsiloxy)phenol (**18**) or *p*-methoxyphenol (**20**). Reaction of **16** with a trace amount of acetic acid in tetrahydrofuran followed by rapid extraction gave a ca. 95:5 mixture of **18** to **20** as determined by ^{1}H NMR spectroscopy. *These results suggest that, in the hydrolysis of the silyl alkyl ketals, the methoxy group leaves first.*



Knowing that the methoxy group is leaving first did not establish the origin of the large rate retardation observed in the hydrolysis of the silyl methyl ketal. However, the literature does offer a convenient rationale. Siloxanes are known to have much weaker basicity toward hydrogen bonding,[5] and aminosilanes are substantially less basic than are the corresponding aliphatic amines in both gas and solution phases.[6] Recently the decreased availability of the electron pairs on a trimethylsiloxy group has been discussed relative to the absence of chelation in Lewis acid catalyzed addition reactions of β-siloxy carbonyl compounds, and calculations were used to support this idea.[7] If such an effect were operative in this case, protonation of the more basic nonbonding electrons on the methoxy oxygen would be favored over protonation of the less basic siloxy oxygen. In addition, if the electron-deficient transition state leading to the carbonium ion intermediate during ketal hydrolysis is more poorly stabilized by the siloxy substituent, a slower rate of hydrolysis could result. Note, however, that for the hydrolysis of an unsymmetrical acetal of formaldehyde, the less basic alcohol was concluded to have left first.[8d]

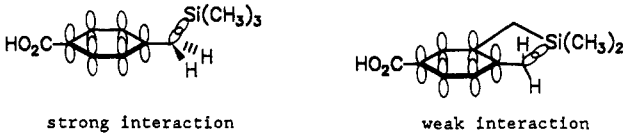
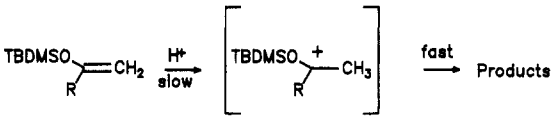


Figure 1. Interaction of carbon–silicon σ-bonds with aromatic π-systems.

Scheme I.[a] **Hydrolysis of *tert*-Butyldimethylsilyl Vinyl Ethers**



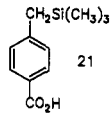
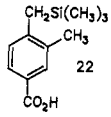
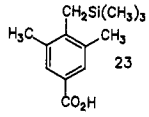
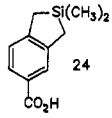
[a] R = H, C_6H_5, *i*-Pr.

An explanation based on the lower basicity of the siloxy oxygen and the poorer ability of a siloxy group to stabilize a positive charge was attractive; however, other experimental evidence conflicted with this idea. The steric effects of a trimethylsiloxy group could also be an important factor in the results of Keck.[7] *In fact, Eliel*[8a-c] *has attributed the absence of chelation of a triisopropylsilyl ether group with Lewis acids as being steric in origin. Theoretical calculations*[9] *tend to discount the importance of the silicon atom delocalizing the electron pairs of an adjacent heteroatom.* In addition, Tidwell et al.[10] have studied the mechanism of hydrolysis of trimethylsilyl vinyl ethers and *tert*-butyldimethylsilyl vinyl ethers.[10] *They concluded that trimethylsilyl vinyl ethers hydrolyze via a rate-determining nucleophilic attack on silicon. However, the corresponding tert-butyldimethylsilyl vinyl ethers hydrolyze by initial rate-determining carbon protonation, giving a silyloxy-stabilized carbonium ion, followed by a fast reaction with water (Scheme I).* This cation would be similar to the intermediate involved in the hydrolysis of silyl methyl ketals. *Why then do the relative hydrolysis rates of methyl vinyl ethers vs those of the corresponding tert-butyldimethylsilyl vinyl ethers differ by only 2.5,*[10] *while a rate difference of nearly 400 was observed for the ketal hydrolyses noted above?*

σ and σ$^+$ Values of Siloxy Groups. One measure of the electron-donating ability of the trialkylsiloxy group would be its σ or σ$^+$ value. Since these values could not be found in the literature, they were measured. The σ value for the *p-tert*-butyldimethylsiloxy group was determined to be –0.24 from the pK_a of the siloxy-substituted benzoic acid. This is very close to the σ value for the *p*-methoxy group (σ –0.27). One possibility was that the σ value for the *p-tert*-butyldimethylsiloxy group was not measuring the electron donation from the oxygen lone-pair electrons but rather from the oxygen–silicon σ-bond. The

(5) West, R.; Wilson, L. S.; Powell, D. L. *J. Organomet. Chem.* **1979**, *178*, 5.
(6) Shea, K. J.; Gobeille, R.; Bramblett, J.; Thompson, E. *J. Am. Chem. Soc.* **1978**, *100*, 1611. Pitt, C. G.; Fowler, M. S. *J. Am. Chem. Soc.* **1967**, *89*, 6792. Sujishi, S.; Witz, S. *Ibid.* **1954**, *76*, 4631.
(7) (a) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (b) Keck, G. E.; Castellino, S. *Ibid.* **1987**, *28*, 281.
(8) (a) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, *27*, 3223. (b) Frye, S. V.; Eliel, E. L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862. (c) See also: Reetz, M. T.; Hullmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600. (d) Salomae, P. *Ann. Acad. Sci. Fenn., Ser. A2* **1961**.
(9) (a) Luke, B. T.; Pople, J. A.; Krogh-Jespersen, M. B.; Apeloig, Y.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1986**, *108*, 260. (b) Oberhammer, H.; Boggs, J. E. *Ibid.* **1980**, *102*, 7241. (c) Aped, P.; Apeloig, Y.; Ellencweig, A.; Fuchs, B.; Goldberg, I.; Karni, M.; Tartakovksy, E. *Ibid.* **1987**, *109*, 1486. For a contrasting view, see ref 7a.
(10) Novice, M. H.; Seikaly, H. R.; Seiz, A. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1980**, *102*, 5835.

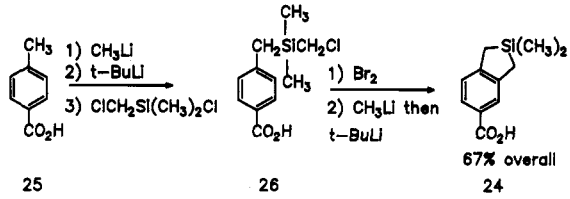
Table II. σ Values for the $CH_2Si(CH_3)_3$ Group in Substituted Systems

entry	compd	pK_a[a]	σ value
1	 21	6.55	−0.29
2	 22	6.70	−0.37[b]
3	 23	6.83	−0.43[b]
4	 24	6.62	−0.29[c]

[a] Values were determined in 70% CH_3CH_2OH/H_2O (v/v) at 25 ± 1 °C. The pK_a of benzoic acid under these conditions was 6.26. [b] Corrected by 0.07 for the contribution of each *m*-methyl group. [c] A correction of 0.07 was applied for the *m*-$CH_2Si(CH_3)_3$ group. If the σ value (0.20) for the *m*-$CH_2Si(CH_3)_3$ is used,[11] the result is even more dramatic.

σ value for the trimethylsilylmethyl group is −0.26;[11] presumably, this is due to interaction of the carbon–silicon σ-bond with the aromatic ring as portrayed in Figure 1.[12]

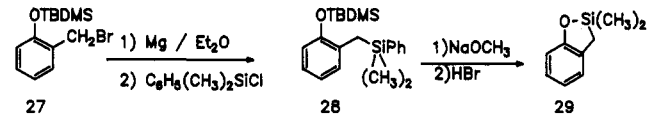
A comparison of the electron-donating ability of a carbon–silicon bond to an oxygen–silicon bond in a selected series of compounds would focus attention on how the siloxy group functions as an electron donor to a π-center, i.e., the carbonium ion formed in the ketal hydrolysis. The acids of entries 1–3 (Table II) were prepared by silylation of the dilithio derivatives of the corresponding *p*-methylbenzoic acid, while **24** (entry 4) was prepared as outlined below.



25 26 24

The pK_a values for these compounds were measured; the results are given in Table II. For the benzylsilanes having *o*-methyl substitution (entries 1–3), a small decrease in the corrected σ values results, presumably reflecting a better average alignment of the benzylic carbon–silicon bond with the π-system due to the presence of the *o*-methyl substituent(s). However, for entry 4 a decrease in donating power results when the benzylic carbon–silicon bond has a poorer alignment with the π-system.

What was required was an analogous series of compounds to evaluate the stereoelectronic requirements for electron donation by a siloxy group. The determination of σ values from ionization of the corresponding benzoic acid was not deemed reliable due to possible hydrolysis of the siloxy group during the base titration. Furthermore, we wished to evaluate the effect of a siloxy group for cases in which more electron demand was placed on the stabilizing center. Thus, a spectroscopic method for determining σ^+ was used to evaluate the overall electron density of the aromatic ring. This involved measurement of the charge-transfer spectra of the indicated compound and tetracyanoethylene.[13] It had been demonstrated previously that the charge-transfer maximum of substituted aromatic compounds correlated directly with σ^+ values determined in the usual manner.[13] However, it would be expected that the Franck–Condon principle would impose a much stronger conformational bias on the values. The compounds chosen for study were prepared by standard methods except for the cyclic ether of entry 7 (Table III), which was prepared as outlined below. Their respective charge-transfer maxima and overall σ^+ values are shown in Table III.



27 28 29

As was anticipated, the σ^+ values measured by this method appear to show a strong dependence on conformation. Thus, the more effective electron-donating ability of a OCH_3 group (entry 4) vs a O-*t*-Bu group (entry 1) results from a better overlap of the ether oxygen nonbonding electrons with the π-system. Models suggest that steric interactions which arise between the bulky O-*t*-Bu group and the ortho hydrogens of the ring twist the ether linkage so that its nonbonding electrons are poorly overlapped with the π-system. The electron-donating ability of the siloxy groups (entries 2 and 3) as measured by this method falls between those of the *tert*-butyl and methyl compounds, an effect that may be largely conformational in origin. The similar charge-transfer absorption maxima for entries 7 and 8 support two contentions. *First, electron donation to the π-system by a siloxy group is nearly as effective as that of an alkoxy group, provided a good conformation for overlap of the oxygen nonbonding electrons with the π-system is present. Second, the mode of interaction of an $OSiR_3$ group with a π-center is different than that of a $CH_2Si(CH_3)_3$ group (compare entries 7 and 8 of Table III with 2 and 4 of Table II). The siloxy interaction involves the nonbonding pair of electrons on oxygen interacting with the π-center while $CH_2Si(CH_3)_3$ interaction arises from the well-known hyperconjugative interaction involving the carbon–silicon bond.*[12]

Discussion

In spite of the literature data presented earlier, these results indicate that the siloxy group is not much different than a methoxy group in its donor ability toward a π-center as measured by σ and σ^+ values. Even the difference in σ^+ values measured herein does not account for the rate retardation observed for hydrolysis of silyl alkyl ketals. However, conformational considerations appear to be very important in the interaction of siloxy groups with π-centers. Thus, the rate retardation associated with the hydrolysis of silyl alkyl ketals in the benzoquinone series appears to have a conformational origin. Evidence strengthening this conclusion would be available if the rates of hydrolysis of silyl alkyl ketals of a simple ketone were available.

Numerous attempts to prepare silyl alkyl ketals of simple ketones via standard procedures failed. Finally, the

(11) Eaborn, C.; Parker, S. H. *J. Chem. Soc.* **1954**, 939.

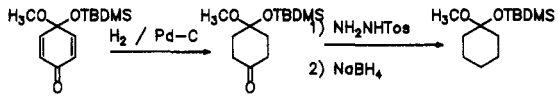
(12) (a) For a discussion of the β-effect of silyl groups, see: Colvin, E. W. *Silicon in Organic Synthesis*; London: Butterworths, 1981. (b) For quantitative studies of the effect in carbonium ion systems, see: Shiner, V. J., Jr.; Ensinger, M. W., Jr.; Rutkowske, R. D. *J. Am. Chem. Soc.* **1987**, *109*, 804 and references cited therein. (c) See also: Lambert, J. B.; Wang, G.-t.; Teramura, D. H. *J. Org. Chem.* **1988**, *53*, 5422.

(13) Hanstein, W.; Berwin, H. J.; Traylor, T. G. *J. Am. Chem. Soc.* **1970**, *92*, 829.

Table III. σ^+ Values Determined from the Charge-Transfer Absorption of the Aromatic Compound and Tetracyanoethylene

entry	ether	ν_{TCNE}	σ^+	entry	ether	ν_{TCNE}	σ^+
1		23750	−0.26	5		20000	−0.67
2		21370	−0.52	6		18380	−0.84
3		20580	−0.60	7		18020	−0.88
4		19720	−0.70	8		17700	−0.91

silyl methyl ketal of cyclohexanone **31** was prepared from **11** via the series of reactions outlined below. This silyl methyl ketal underwent hydrolysis at nearly the same rate as did the dimethyl ketal of cyclohexanone. This result is in agreement with the previous studies of *tert*-butyldimethylsiloxy vinyl ether hydrolysis and suggests that the rate retardation observed for silyl methyl ketals in quinone bisketals is unique to these systems.

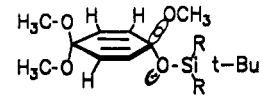


11 30 31

Examination of the possible conformations of the silyl methyl bisketal indicates that the most favorable conformation for **10** is that in which the bulky trialkylsilyl group is directed from the cyclohexadiene ring (Figure 2). In this conformation, (1) stabilization of the electron-deficient ketal carbon by the nonbonding electrons on the siloxy oxygen during the rate-determining cleavage of the carbon–methoxy bond is very poor, and (2) rotation of the trialkylsiloxy group into a conformation allowing maximum overlap is inhibited by hydrogen atoms on the carbons adjacent to the ketal carbon. In this rationale, steric inhibition in achieving a good conformation for stabilization of the incipient positive charge is the most important factor in controlling the hydrolysis rate of the silyl methyl linkage in quinone bisketals.

Experimental Section[14]

General Procedure for Kinetics of Bisketal Hydrolysis. To a 25 °C solution of the bisketal in THF (1.50 mL) in a capped UV cell in the thermostated chamber of a Beckman DU-7 ultraviolet spectrophotometer was added a 2.50 M aqueous solution of acetic acid (0.70 mL) at 25 °C, giving a final bisketal concentration of 5.18×10^{-4} to 16.7×10^{-4} M. The rate constants were determined for each bisketal by assaying the monoketal produced by the increase in the optical density at an appropriate wavelength (253 or 279 nm). The rate constants were determined from the slope of a plot of log A/A_0 vs time, using the infinity optical density for the value of A_0. The plots showed excellent linearity through 3 half-lives with correlation coefficients typically 0.999. For all compounds, the rates reported are the average of two or three independent determinations. The rate for benzoquinone tetramethyl bisketal was 9.85×10^{-3} s^{-1} (uncorrected for two ketals undergoing hydrolysis) with an estimated error of <5%. The absolute rate constants for the other ketal hydrolyses can be calculated from the rate constant above and the relative rate values in Table I.



R = CH_3, C_6H_5

Figure 2. Attempted depiction of the poor overlap in the siloxy electrons with the developing carbonium ion center.

Ethylene *tert*-Butyldiphenylsilyl Methyl Bisketal of Benzoquinone (14). To a base-washed flask were added the mixed bisketal **12** (0.767 g, 1.81 mmol) and THF (9 mL). When the starting material had dissolved, ethylene glycol (3 mL, distilled from $CaSO_4$) was added. After cooling to 0 °C, *p*-toluenesulfonic acid (5.5 mg) dissolved in THF (1 mL) was added all at once to the solution. The reaction was quenched after 20 s with 5% $NaHCO_3$ (1 mL), and the solution was poured into water (75 mL) and extracted three times with CH_2Cl_2 (3 × 25 mL). Workup gave nearly pure bisketal (0.74 g), which was further purified by silica gel chromatography (12 × 2 cm column, PE through 7% Et_2O/PE as eluant) affording the monoethylene glycol bisketal (0.556 g, 73%) as an oil that solidified upon standing. A small amount was recrystallized from CH_3OH for analysis: mp 53–53.5 °C; IR (NaCl plate) 1410 (m), 1115 (s, br), 1065 (m), 1020 (m), 970 (s), 700 cm^{-1} (s); ^{1}H NMR δ 7.77–7.62 (m, 4 H), 7.43–7.30 (m, 6 H), 5.82 (J_{AB} = 10.4 Hz, 2 H), 5.69 (J_{AB} = 10.4 Hz, 2 H), 3.97 (br s, 4 H), 3.12 (s, 3 H), 1.01 (s, 9 H); mass spectrum, exact mass calcd for $C_{25}H_{30}O_4Si$ *m/e* 422.1914, obsd 422.1871.

Reduction/Elimination of 11. To a solution of 4-methoxy-4-(*tert*-butyldimethylsiloxy)-2,5-cyclohexadienone (**11**) (0.187 g, 0.736 mmol) in CH_3CH_2OH was added finely ground $NaBH_4$ (55 mg, 2.1 mmol). After 5 min, the mixture was poured into water (30 mL) and extracted with Et_2O (3 × 10 mL). The combined Et_2O portions were washed with water (5 mL) dried through a cone of $CaSO_4$, and concentrated, affording a pale yellow oil (0.180 g), which was a stereoisomeric mixture, **16**, by IR and ^{1}H NMR spectroscopy. Next, THF (10 mL) and acetic acid (10 μL) were added, and the solution was stirred for 5 min at room temperature. The solution was then poured into 5% $NaHCO_3$ (20 mL) and extracted with Et_2O (10 mL). Workup gave a pale yellow oil (0.151 g, 92% for two steps). ^{1}H NMR and IR analyses indicated that the oil was about 95% silyl ether and 5% *p*-methoxyphenol.

4-[(Trimethylsilyl)methyl]benzoic Acid. To a solution of *p*-toluic acid (1.00 g, 7.35 mmol), THF (25 mL), and HMPA (2.64 mL) at −78 °C was added a solution of LDA (18 mmol) in THF.

(14) Melting points were determined in capillaries in a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 283B spectrometer on KBr disks unless otherwise noted. Routine ^{1}H NMR spectra were determined at 80 MHz on an IBM NR 80 spectrometer using deuteriochloroform as solvent and residual chloroform or tetramethylsilane as internal standard. Mass spectral and exact mass measurements were obtained by Richard Weisenberger on a Kratos MS-30 spectrometer. Alumina and silica gel (230–400 mesh) were obtained from E. Merck Co. Tetrahydrofuran was purified by distillation from benzophenone ketyl. Thin-layer chromatography (TLC) was done by using Merck silica gel 60 F_{254} precoated aluminum-backed plates, 0.2-mm thickness. Throughout the Experimental Section, the following abbreviations are used: petroleum ether, bp 35–60 °C (PE), diethyl ether (Et_2O), tetrahydrofuran (THF), *tert*-butyldimethylsilyl (TBDS), *tert*-butyldiphenylsilyl (TBDPS). Unless otherwise noted, "bisketal" and "monoketal" refer to *benzoquinone* bisketal and *benzoquinone* monoketal, respectively. All reactions involving organolithium compounds were done under a nitrogen atmosphere. Standard workup consisted of washing the organic phase with water (CH_2Cl_2) or brine (Et_2O), drying over sodium sulfate, and then placing the resultant material under <0.5 Torr until the weight was constant.

The solution turned dark yellow, and after being stirred for 10 min, the reaction was quenched with trimethylsilyl chloride (1.62 g, 15 mmol). As the mixture was allowed to warm to room temperature, the dark yellow color faded to light green and then to pale yellow. The mixture was poured into water (70 mL) and extracted with Et_2O (3 × 20 mL). The combined Et_2O portions were extracted with 5% Na_2CO_3 (3 × 25 mL), and the combined Na_2CO_3 portions were carefully acidified with 6 M HCl and extracted with Et_2O (3 × 25 mL). Workup gave the title compound (1.55 g). Recrystallization from CH_3OH/H_2O afforded the title acid (1.1 g, 72%), mp 178–179 °C (lit.[11] mp 179 °C).

3-Methyl-4-[(trimethylsilyl)methyl]benzoic Acid. To a solution of 3,4-dimethylbenzoic acid (1.00 g, 6.66 mmol), HMPA (2.40 mL), and THF (40 mL) at −78 °C were added methyllithium (8.00 mL, 0.84 M in Et_2O, 6.7 mmol) and then *tert*-butyllithium (3.70 mL, 1.8 M in pentane, 6.7 mmol). After the red-brown solution had been stirred for 5 min, trimethylsilyl chloride (2.0 mL, 1.7 g, 16 mmol) was added all at once, yielding a tan-colored solution, which was allowed to warm to room temperature and then was stirred for 3 h. The THF was removed under reduced pressure, Et_2O (100 mL) was added, and the solution was washed with 1 M HCl (4 × 50 mL). Workup as for the reaction above gave a white solid (1.25 g, 85%), mp 113–119 °C. One recrystallization from aqueous methanol afforded a white crystallization solid (0.90 g): mp 125–127 °C (61%); IR (KBr) 2950 (m), 1680 (s), 1608 (m), 1432 (m), 1317 (m), 1300 (m), 1275 (m), 1245 (m), 1155 (m), 850 (m), 840 cm^{-1} (m); ^1H NMR δ 7.87 (br s, 1 H), 7.82 (br d, partially obscured, J_{AB} = 7.9 Hz, 1 H), 7.04 (br d, J_{AB} = 7.9 Hz, 1 H), 2.28 (s, 3 H), 2.20 (s, 2 H), 0.02 (s, 9 H); mass spectrum, exact mass calcd for $C_{12}H_{18}O_2Si$ m/e 222.1076, obsd 222.1078.

3,5-Dimethyl-4-[(trimethylsilyl)methyl]benzoic Acid. To a solution of 3,4,5-trimethylbenzoic acid (1.00 g, 6.09 mmol), THF (40 mL), and HMPA (2.12 mL, 2.18 g) at −78 °C was added *tert*-butyllithium (7.00 mL, 1.74 M in pentane, 12.18 mmol) via syringe at a slow stream. As the second equivalent was added, the solution turned brown. The dianion was stirred for 2 min, and then the reaction was quenched rapidly with chlorotrimethylsilane (1.55 mL, 1.33 g, 12.2 mmol), dissipating the color. The pale yellow solution was allowed to warm to room temperature and then was stirred for 2 h. Workup as for the reaction above gave a white solid (1.10 g). Recrystallization from CH_3OH/H_2O afforded white crystals (0.937 g, 65%): mp 162–164 °C; IR (KBr) 2955 (m), 1680 (s), 1601 (m), 1425 (m), 1300 (s), 1240 (s), 1192 (m), 840 cm^{-1} (br, s); ^1H NMR δ 7.74 (s, 2 H), 2.29 (s, 6 H), 2.26 (s, 2 H), 0.04 (s, 9 H); mass spectrum, exact mass calcd for $C_{13}H_{20}O_2Si$ m/e 236.1233, obsd 236.1239.

4-[[(Chloromethyl)dimethylsilyl]methyl]benzoic Acid (26). To a solution of HMPA (7.16 mL), THF (100 mL), and *p*-toluic acid (2.72 g, 20 mmol) at −78 °C were added methyllithium (24 mL, 0.83 M in Et_2O, 20 mmol) and *tert*-butyllithium (11 mL, 1.8 M in pentane, 19.8 mmol), generating a dark yellow dianion. After stirring for 5 min, chloro(chloromethyl)dimethylsilane (5.27 mL, 40 mmol) was added, resulting in a pale yellow solution, which was allowed to warm to room temperature and then was stirred for 2 h. Workup as above gave a white solid (4.45 g, 92%). A small amount recrystallized from CH_3OH/H_2O showed the following characteristics: mp 140–140.5 °C; IR (KBr) 2960 (br), 1685 (s), 1610 (s), 1425 (m), 1320 (m), 1292 (m), 860 (m), 840 cm^{-1} (m); ^1H NMR δ 8.00 (d, J_{AB} = 8.3 Hz, 2 H), 7.14 (d, J_{AB} = 8.3 Hz, 2 H), 2.74 (s, 2 H), 2.35 (br s, 2 H), 0.13 (s, 6 H); mass spectrum, exact mass calcd for $C_{11}H_{15}ClO_2Si$ m/e 242.0503, obsd 242.0509.

3-Bromo-4-[[(chloromethyl)dimethylsilyl]methyl]benzoic Acid. Finely divided 4-[[(chloromethyl)dimethylsilyl]methyl]-benzoic acid (**26**) (2.0 g, 8.3 mmol) and bromine (4 mL) were stirred at room temperature in an open 25-mL flask for 1 h. The thick mixture was poured into ice (10 g) and Et_2O (100 mL). The excess bromine was carefully destroyed with portions of 10% Na_2SO_3. Extractive workup with Et_2O gave a white solid (2.4 g, 90%), mp 120–124 °C. Recrystallization from Et_2O/PE afforded a white powder (2.25 g, 85%): mp 125–125.6 °C; IR (KBr) 3000 (br, m), 1690 (s), 1600 (m), 1420 (m), 1310 (m), 1260 (s), 1150 (m), 840 cm^{-1} (m); ^1H NMR δ 8.27 (d, J = 1.8 Hz, 1 H), 7.93 (dd, J_{AB} = 7.7 Hz, 1.8 Hz, 1 H), 7.22 (d, J_{AB} = 7.7 Hz, 1 H), 2.83 (s, 2 H), 2.58 (br s, 2 H), 0.17 (s, 6 H); mass spectrum, exact mass calcd for $C_{11}H_{14}BrClO_2Si$ m/e 321.9615, obsd 321.9624.

[(1-Carboxy-3,4-phenylene)dimethylene]dimethylsilane (24). To a solution of 3-bromo-4-[[(chloromethyl)dimethylsilyl]methyl]benzoic acid (1.510 g, 4.704 mmol) and THF (100 mL) at −78 °C was added methyllithium (5.6 mL, 4.7 mmol) until the solution turned a light yellow color. Next, *tert*-butyllithium (5.50 mL, 9.90 mmol) was added in a steady stream, turning the solution dark yellow. After stirring for 5 min, water (1 mL) was added rapidly, causing the dark solution to turn cloudy white. When the mixture had warmed to room temperature, a 1 M HCl solution saturated with NaCl (50 mL) and PE (50 mL) were added, and the mixture was shaken and separated. The aqueous layer was washed with Et_2O (25 mL), which was added to the PE portion. Workup gave a white solid (0.88 g), mp 160–170 °C. Recrystallization from CH_3OH/H_2O gave **24** (0.83 g, 86%, two crops) as white crystals: mp 177–179 °C; IR (KBr) 2950 (br, s), 1680 (s), 1600 (m), 1560 (m), 1430 (sh, m), 1410 (m), 1310 (m), 1290 (m), 1360 (m), 1125 (m), 900 (m), 840 (m), 820 cm^{-1} (m); ^1H NMR δ 7.96 (br s, 1 H), 7.83 (br d, J_{AB} = 8.5 Hz, 1 H), 7.31 (br d, J_{AB} = 8.5 Hz, 1 H), 2.10 (br s, 4 H), 0.24 (s, 6 H); mass spectrum, exact mass calcd for $C_{11}H_{14}O_2Si$ m/e 206.0763, obsd 206.0765.

General Procedure for pK_a Determinations and σ Values. The appropriate acid (approximately 1 mmol) was accurately weighed and dissolved in absolute CH_3CH_2OH (14 mL), and then distilled water (6 mL) was added. The solutions were equilibrated to 25 °C and then titrated with a 0.0813 M solution of NaOH in 70% CH_3CH_2OH/H_2O standardized against potassium acid phthalate.[15] The titrations were followed with a Fisher Scientific pH electrode (13-369-104) calibrated periodically to pH 4 and pH 7, and the pK_a values were calculated according to the procedure described by Meites and Thomas.[16] Since the σ value for *p*-$CH_2Si(CH_3)_3$ determined from the difference in pK_a values in this solvent was in reasonable agreement with the literature[11] value, no solvent corrections were applied to the σ values reported.

***o*-(*tert*-Butyldimethylsiloxy)benzyl Bromide (27).** To a solution of *o*-cresol silyl ether (18 g, 81.1 mmol) and CCl_4 (100 mL) was added NBS (16.0 g, 90 mmol), and the mixture was brought to reflux by placing two 150-W incandescent lights in contact with the flask. After heating to reflux, azobis(isobutryonitrile) (200 mg) was added in 2 portions, and an exothermic reaction occurred. The mixture was maintained at reflux for 10 min after the exothermic reaction subsided (about 5 min), then cooled, and filtered. The CCl_4 solution was washed with water (100 mL) and worked up to give a light orange oil (25 g). Short-path distillation (92–100 °C/0.7 Torr) afforded a colorless oil (22 g, 90%): IR (NaCl plate) 2960 (m), 2930 (m), 2860 (m), 1600 (m), 1490 (s), 1470 (m), 1455 (m), 1280 (sh, s), 1270 (s), 925 (s), 840 (s), 825 (s), 780 (s), 750 cm^{-1} (s); ^1H NMR δ 7.39–6.75 (m, 4 H), 4.53 (s, 2 H), 1.05 (s, 9 H), 0.29 (s, 6 H); mass spectrum, exact mass calcd for $C_{13}H_{20}OSiBr$ m/e 301.0446, obsd 301.0459.

[[*o*-(*tert*-Butyldimethylsiloxy)phenyl]methyl]dimethylphenylsilane (28). To a mixture of anhydrous ether (20 mL) and magnesium (granular, 7 g, 290 mmol) in a three-necked, 250-mL flask equipped with a dry ice condenser, N_2 inlet, dropping funnel, and magnetic stirrer were added a few drops of ethylene dibromide. When the vigorous gas evolution subsided, pure *o*-(*tert*-butyldimethylsiloxy)benzyl bromide (about 1 mL) was added, causing a vigorous reaction. The remaining benzyl bromide (21.88 g, 72.7 mmol total) was added as an Et_2O solution (40 mL) from the addition funnel over a 3-h period. When the exothermic reaction subsided, the solution was refluxed for an additional 15 min, allowed to cool, and transferred via pressure gradient to a stirring solution of chlorodimethylphenylsilane (12 g, 70.3 mmol) and Et_2O (50 mL). The mixture became warm and was cooled in ice to prevent boiling. After 3 h, the reaction mixture was cautiously hydrolyzed with water (50 mL) (exothermic!) and then partitioned between water (50 mL) and PE (50 mL). Workup gave an orange oil (23.3 g, 90%), which was a mixture of benzylsilane and bibenzyl (4:1) by ^1H NMR analysis (some siloxane was also present). Most of the siloxane was removed by Kugelrohr distillation at 125 °C/1 Torr, and this material was used directly in the next step. A small sample was chromatographed on silica

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gel for analysis and showed the following characteristics: IR (NaCl plate) 2950 (m), 2930 (m), 2850 (m), 1490 (s), 1450 (m), 1250 (s), 1110 (m), 925 (s), 845 (s), 775 (s), 750 (m), 725 (m), 690 cm^{-1} (m); ^1H NMR δ 7.46–7.25 (m, 5 H), 6.95–6.20 (m, 4 H), 2.30 (s, 2 H), 0.99 (s, 9 H), 0.23 (s, 6 H), 0.20 (s, 6 H); mass spectrum, exact mass calcd for $C_{21}H_{32}OSi_2$ m/e 357.2061, obsd 357.2071.

[(*o*-Hydroxyphenyl)methyl]dimethylphenylsilane. To a mixture of the crude benzylsilane from above (3.0 g, 8.42 mmol) and CH_3OH (20 mL) was added $NaOCH_3$ (3 g, 56 mmol). The slurry was stirred vigorously for 3 h, then poured into water (40 mL), and made slightly acidic to litmus with a 6 M solution of HCl. The phenol was extracted with Et_2O (3 × 25 mL), and the combined Et_2O was worked up to give the phenol as an orange oil contaminated with desilylated bibenzyl from the Grignard reaction. Chromatography on silica gel (4 × 10 cm column, 10% Et_2O/PE as eluant) afforded the phenol (1.24 g) as a pale yellow oil (61%): IR (NaCl plate) 3530 (m, br), 1500 (m), 1490 (m), 1455 (s), 1425 (m), 1250 (s), 1220 (m, sh), 1170 (m), 1155 (m), 1110 (s) 850 (s), 830 (s), 750 (s), 730 (s), 695 cm^{-1} (s); ^1H NMR δ 7.53–7.30 (m, 5 H), 6.97–6.63 (m, 4 H), 4.29 (s, 1 H), 2.28 (s, 2 H), 0.28 (s, 6 H); mass spectrum, exact mass calcd for $C_{15}H_{18}OSi$ m/e 242.1127, obsd 242.1121.

2,2-Dimethyl-2-silabenzofuran (29). Dry HBr was bubbled continuously through a stirred solution of the phenol (1.015 g, 4.194 mmol) and $CHCl_3$ (25 mL) for 2 h at 25 °C. Next, a stream of dry nitrogen was passed over the reddish solution which was warmed to 45 °C until the solution volume was ca. 5 mL. Continued concentration in vacuo, followed by molecular distillation (1.5 Torr, bath 78 °C), gave the cyclic silyl ether **29** (490 mg, 71%). The IR spectrum of this oil showed an OH stretch, indicating some decomposition of the silyl ether. An analytical sample was obtained by preparative GLPC (12 × 0.125 in. column, 5% OV-101, Chromosorb W/HP 80/100 mesh, temperature programmed from 140 to 180 °C): IR (NaCl plate) 1600 (m), 1580 (m), 1480 (s), 1460 (s), 1280 (m), 1260 (s), 1230 (s), 1125 (s), 875 (s), 850 (s), 825 (s), 750 cm^{-1} (s); ^1H NMR δ 7.17–6.72 (m, 4 H), 2.07 (s, 2 H), 0.40 (s, 6 H); mass spectrum, exact mass calcd for $C_9H_{12}OSi$ m/e 164.0657, obsd 164.0669.

1,4-Cyclohexanedione *tert*-Butyldimethylsilyl Methyl Ketal (30). To a slurry of 5% Pd/C (0.1 g) in absolute CH_3CH_2OH (20 mL) was added methyl silyl quinone monoketal (2.00 g, 7.87 mmol), and the mixture was hydrogenated in a Parr apparatus at a pressure of 60 psig for 1 h. Workup gave the cyclohexanedione monoketal (2.01 g, 99%), pure by ^1H NMR analysis. An analytical sample was obtained by GLPC (120 × 0.125 in. column, 5% OV-101 on Chromosorb W, 150 °C): IR (NaCl plate) 2960 (m), 2930 (m), 1725 (s), 1255 (m), 1130 (m), 1100 (m), 1055 (m), 835 (m), 775 cm^{-1} (m); ^1H NMR δ 3.32 (s, 3 H), 2.5–2.3 (br, 4 H), 2.2–1.9 (br, 4 H), 0.91 (s, 9 H), 0.15 (s, 6 H); mass spectrum, exact mass calcd for $C_{12}H_{23}O_2Si$ ($M^+ - CH_3O$) m/e 227.1467, obsd 227.1490.

Cyclohexanone *tert*-Butyldimethylsilyl Methyl Ketal (31). To solution of cyclohexanedione monoketal (0.500 g, 1.94 mmol) and CH_3OH (5 mL) was added (*p*-tolylsulfonyl)hydrazine (0.400 g, 2.15 mmol). TLC analysis showed that hydrazone formation was complete after 15 min. The solution was cooled to 0 °C, and $NaBH_4$ (0.4 g, 10 mmol) was added cautiously in portions. When gas evolution subsided, the mixture was heated to reflux for 2 min, cooled, poured into water (30 mL), and extracted with hexane (2 × 15 mL). Workup gave the cyclohexanone methyl silyl ketal (0.400 g, 85%) as a clear oil, containing only minor, volatile impurities by GC analysis (0.125 × 12 in. column, 5% OV-101 on Chromosorb W, 140 °C). Preparative GC (same column/conditions) afforded the analytical sample: IR (NaCl plate) 2940 (s), 2860 (s), 1250 (s), 1105 (s), 1055 (s), 1000 (s), 830 (s), 770 cm^{-1} (s); ^1H NMR δ 3.20 (s, 3 H), 1.7–1.3 (br, 10 H), 0.89 (s, 9 H), 0.11 (s, 6 H); mass spectrum, exact mass calcd for $C_{13}H_{28}O_2Si$ m/e 244.1858, obsd 244.1851.

General Procedure for Kinetics of Cyclohexanone Ketal Hydrolysis. To a 25 °C solution of THF (0.75 mL) and 15% aqueous acetic acid (0.50 mL) in a capped UV cell was injected the ketal, giving a final bisketal concentration of ca. 0.01 M. The mixture was stirred and placed into the spectrophotometer, and the increase in the optical density was monitored at 295 nm. The rate constants were determined as described above. The rate constant measured for the methyl *tert*-butyldimethylsilyl ketal of cyclohexanone under these conditions was 8.23×10^{-2} s^{-1} while that for the dimethyl ketal of cyclohexanone was 7.15×10^{-2} s^{-1}.

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Supplementary Material Available: Preparation of 3-bromo-4,5-dimethylbenzoic acid, 3,4,5-trimethylbenzoic acid, *p*-(*tert*-butyldimethylsiloxy)benzaldehyde, *p*-(*tert*-butyldimethylsiloxy)benzoic acid, and *o*-cresol *tert*-butyldimethylsilyl ether and representative kinetic data and plots (6 pages). Ordering information is given on any current masthead page.

Bacterial Sterol Surrogates. Determination of the Absolute Configuration of Bacteriohopanetetrol Side Chain by Hemisynthesis of Its Diastereoisomers

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The 32*R*,33*R*,34*S* configuration of the side chain of bacteriohopanetetrol, a representative compound of a wide-spread bacterial triterpenoid series, was established by correlation with the eight synthetic stereoisomers.

Triterpenoids derived from the pentacyclic hopane skeleton (1) or hopanoids are widely distributed in bacteria[1] and were first known from their ubiquitous molecular fossils in the organic matter of all sedimentary rocks.[2] Numerous experiments performed on biological membrane models as well as on several biological systems have shown that the prokaryotic hopanoids act much more like the sterols from eukaryotes, i.e. as membrane stabilizers.[3]

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