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A Synthesis of the C_6,C_{11}-Dideoxyanthracyclinone Skeleton via Hassall Cyclization and Oxidative Desilylation

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A sequence of regiocontrolled Diels–Alder reactions has been used to prepare **15**. Oxygenation of the benzylic silane in the presence of a fluoride source introduces the C_7 hydroxyl group (95%). Further conversion to the nitrile **21** followed by base-induced Hassall cyclization and oxidation gives the anthraquinone **25**. Deprotection can be effected, but attempts to prepare **28** result in low yields. The oxygenation can be extended to certain enol silanes, but protodesilylation is a serious side reaction.

The decreased cardiotoxocity[1] of anthracycline antibiotics lacking an oxygen function at C_6 or at C_{11} has stimulated extensive synthetic effort in this area.[2] We report the results of an investigation directed at the synthesis of a family of analogues lacking oxygen substituents at both C_6 and C_{11}. The approach allows control of regiochemistry in rings A and B via Diels–Alder synthesis and uses the Hassall cyclization[3,4] to close ring C. A benzylic silicon substituent at C_7 is converted into benzylic hydroxyl group by fluoride-initiated oxygenation as a key step in this strategy.

The synthetic approach is dictated by reliance on the Hassall cyclization[3] (Figure 1). In principle, this reaction solves the problem of regiocontrolled construction of the ring B,C,D subunit, and the strategy depends on the synthesis of a highly substituted ring A,B subunit. The generalized approach suggested in Figure 1 assumes the presence of oxygen substituents at C_7 and C_9, as well as the typical two-carbon side chain at C_9. This specific combination of substituents has not yet been tested in a Hassall cyclization, although it may reasonably be expected to survive the strongly basic conditions. The approach described below uses a simple ketal function at C_9 instead of the tertiary C_9 alcohol to avoid issues of relative stereochemistry.

As in a preliminary study,[4] the A,B ring segment was prepared by Diels–Alder synthesis using acetylenic dienophiles. In the first stage, the 1,4-dihydrobenzene derivative **1** could be obtained without difficulty starting from propiolonitrile and a silyl-substituted alkoxybutadiene (Figure 2). Other dienophiles such as methyl propiolate or propiolaldehyde could also be used, but the derived adducts could not be selectively ketalized, as in the highly efficient conversion from **1** to **2**. Further elaboration of the side chain via Dibal reduction to aldehyde **3** and Horner–Emmons chain extension to **4** proved routine, as

(1) (a) For review of anthracycline cardiotoxicity, see: Kantrowitz, N. E.; Bristow, M. R. *Prog. Cardiovasc. Dis.* **1984**, *27*, 195–200. Ferrans, V. J. *Adv. Exp. Med. Biol.* **1983**, *161*, 519–532. (b) Wheeler, D. M. S. *Cancer Chemother. Rep., Part 1* **1975**, *59*, 258. (c) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; Vol. 1, pp 63–132. Brown, J. R.; Imam, S. H. *Prog. Med. Chem.* **1984**, *21*, 169–236. Arcamone, F. *Med. Res. Rev.* **1984**, *4*, 153–188. Menozzi, M.; Vannini, E.; Valentini, L.; Penco, S.; Arcamone, F. *Stud. Biophys.* **1984**, *104*, 113–119. *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982. *Anthracyclines: Current Status and New Developments*; Crooke, S. T., Reich, S. D., Eds.; Academic Press: New York, 1980. Arcamone, F. *Doxorubicin*; Academic Press: New York, 1981. Arcamone, F. In *Structure–Activity Relationships of Antitumor Agents*; Reinhoudt, D. N., Connors, T. A., Pinedo, H. M., van de Poll, K. W., Eds.; Martinus Nijhoff: The Hague, 1983; pp 111–133.

(2) Reviews: Swenton, J. S. In *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982; pp 167–196. Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Chem. Ind. (London)* **1985**, 106–112. Arcamone, F. *Bull. Soc. Chim. Belg.* **1982**, *91*, 1003–1017. Kelly, T. R. *Ann. Rep. Med. Chem.* **1979**, *14*, 288–298. Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790. For some recent syntheses of 6-deoxyanthracyclinones, see: Kraus, G. A.; Hagen, M. D. *J. Org. Chem.* **1985**, *50*, 3252–3255. Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1862–1863. Angelucci, F.; Arcamone, F.; Barchielli, G.; Suarato, A.; Vanotti, E.; Penco, S. *J. Chem. Soc., Chem. Commun.* **1984**, 530–531. Penco, S.; Angelucci, F.; Ballabio, M.; Barchielli, G.; Suarato, A.; Vanotti, E.; Vigevani, A.; Arcamone, F. *Heterocycles* **1984**, *21*, 21–28. Penco, S.; Angelucci, F.; Ballabio, M.; Barchielli, G.; Suarato, A.; Vanotti, E.; Vigevani, A.; Arcamone, F. *Tetrahedron* **1984**, *40*, 4677–4683. Boeckman, R. K., Jr.; Cheon, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 4112–4113. Penco, S.; Angelucci, F.; Arcamone, F.; Ballabio, M.; Barchielli, G.; Franceschi, G.; Franchi, G.; Suarato, A.; Vanotti, E. *J. Org. Chem.* **1983**, *48*, 405–406. Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Nouv. J. Chim.* **1983**, *7*, 205–211. Kende, A. S.; Gesson, J.-P.; Demuth, T. P. *Tetrahedron Lett.* **1981**, *22*, 1667–1670.

(3) Davies, J. S.; Davies, V. H.; Hassall, C. H. *J. Chem. Soc. C* **1969**, 1873–1879. Hassall, C. H.; Morgan, B. A. *J. Chem. Soc. D* **1970**, 1345. Hassall, C. H.; Morgan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2853–2861.

(4) Vedejs, E.; Miller, W. H.; Pribish, J. R. *J. Org. Chem.* **1983**, *48*, 3611–3613.

0022-3263/88/1953-1593$01.50/0

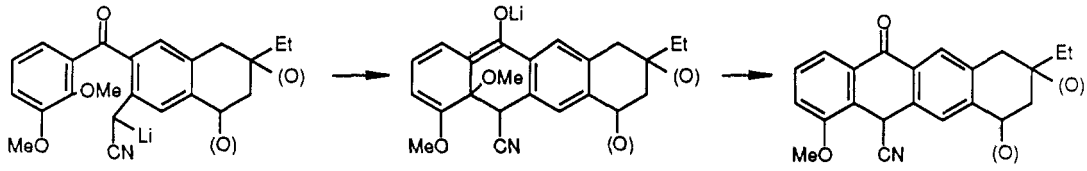

Figure 1.

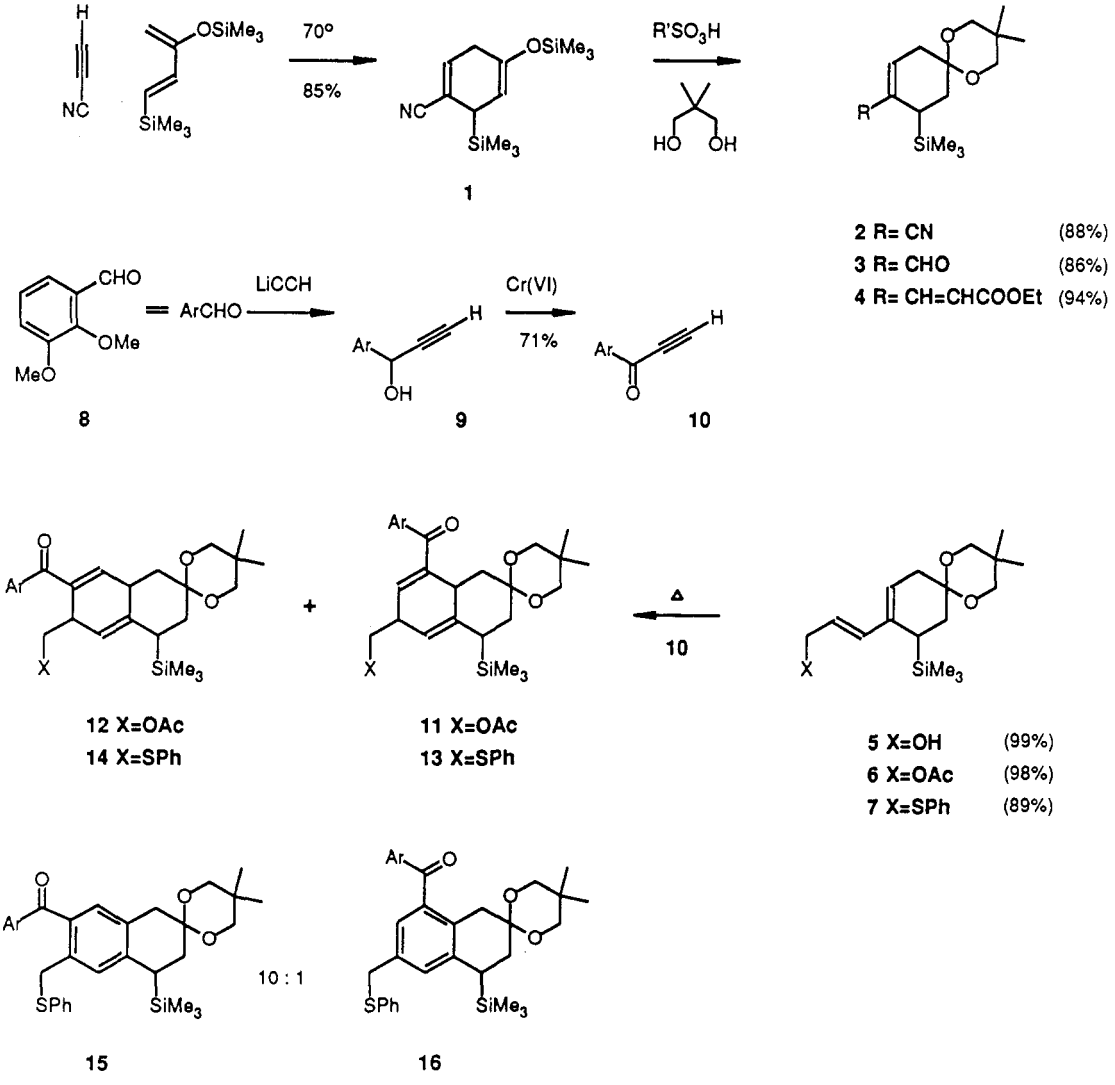

Figure 2.

did the Dibal reduction to the diene alcohol **5**. The important issue of regiocontrolled Diels–Alder synthesis of the B ring was now at hand.

In the earlier study,[4] we had observed that the now familiar directing effect of allylic silicon[5] can overcome the directing influence of other substituents. Not surprisingly, the same result was observed with derivatives of **5**. The acetate **6**, obtained via Steglich acylation from **5**, reacted with a 6:1 preference for regioisomer **12** over **11** (each formed as a mixture of two stereoisomers). An improved 10:1 ratio in the desired direction was obtained by using the corresponding sulfide **7** which was prepared in one step from **5** with the Bu_3P/N-(phenylsulfenyl)succinimide reagent.[6] The adducts **14** and **13** could not be purified due to the presence of two diastereomers of each, but DDQ-induced aromatization produced **15** which could be separated from the minor isomer **16**.

Adduct **15** resembles the typical Hassall substrates and has the necessary anion-stabilizing benzylic substituent. However, attempts to induce cyclization directly from **15** (or the sulfoxide or the sulfone) resulted in decomposition products lacking the ring-A silicon substituent. Apparently, the strongly basic catalysts (dimsyl anion; KHMDS; etc.) had induced nucleophilic attack at the silicon due to activation by a para aroyl substituent. We had initially planned to convert the benzylic silicon into hydroxyl near the end of the synthesis, a strategy that is conceptually related to that developed by Garland et al.[7] However, the phenolic hydroxyl activating effect required in Garland's case ($Pb[OAc]_4$ oxidation) would not be present at any stage in the synthesis of C_6,C_{11}-dideoxyanthracyclinone. Nucleophilic activation of silicon in the oxidation step had

(5) Wilson, S. R.; Phillips, L. R.; Natalie, K. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 3340. Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 355. Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534.
(6) Walker, K. A. M. *Tetrahedron Lett.* **1977**, 4475–4478.
(7) Garland, R. B.; Palmer, J. R.; Schulz, J. A.; Sollman, P. B.; Pappo, R. *Tetrahedron Lett.* **1978**, 3669.

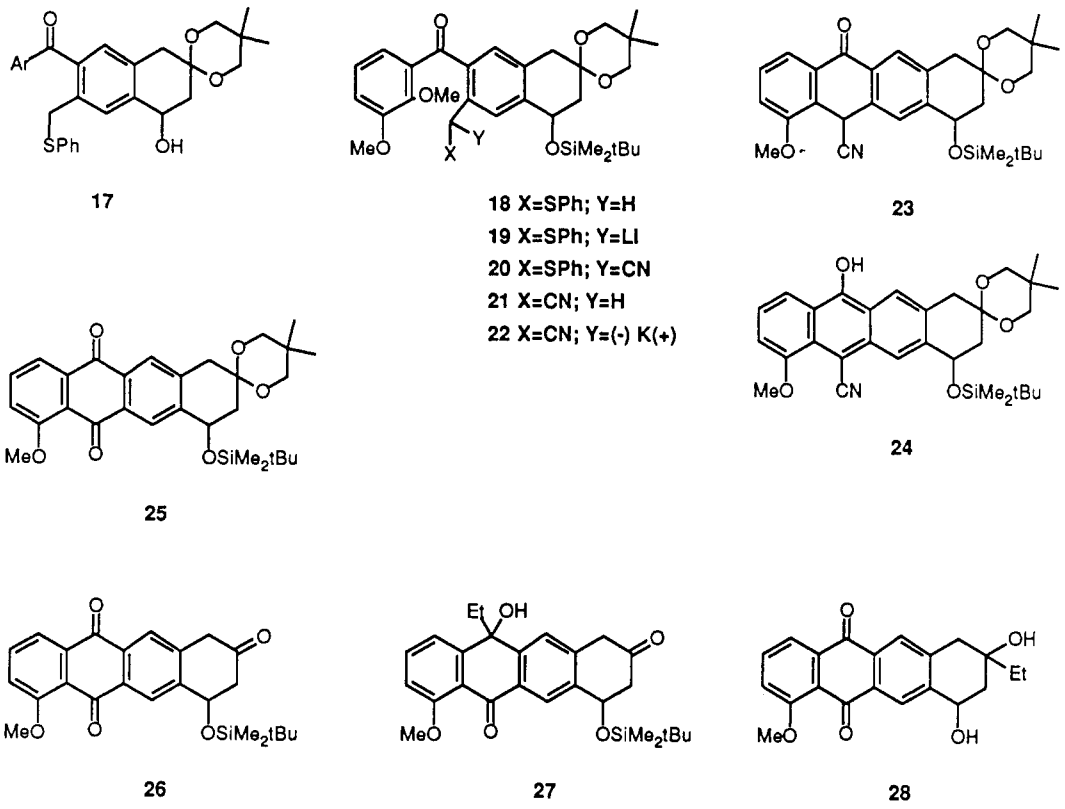

Figure 3.

been planned in our case, and it became clear that oxidative desilylation would have to precede the Hassall cyclization.

The crucial transformation to **17** was achieved in a reproducible yield of 95% by treatment of **15** with TAS fluoride (TASF)[8] $(Me_2N)_3S^+Me_3SiF_2^-$ in acetonitrile at −37 °C in the presence of oxygen and trimethyl phosphite. Use of Ph_3P in place of the phosphite resulted in 60–70% yields of **17** and the formation of polar byproducts, while reactions performed without any phosphorus reagent present as peroxide scavenger were highly complex. Slower reactions were noted in ether solvents (THF, DME), probably due to the low solubility of TASF. Other fluoride sources proved ineffective, and various forms of $Bu_4N^+F^-$ or $PhCH_2NMe_3^+F^-$ resulted in predominant conversion of **15** into the corresponding structure with a proton in place of silicon. The mechanism of the activation step presumably involves the formation of the benzylic anion (a conjugated enolate with respect to the para aroyl group) or of the corresponding pentacoordinated silicon anion species resulting from the initial addition of fluoride to silicon. Interaction with molecular oxygen leads to a benzylic hydroperoxide anion (or its *O*-silyl derivative), and eventual reduction by phosphite affords the alcohol **17** (Figure 3).

After hydroxyl protection as the *tert*-butyldimethylsilyl ether **18**, several cyclization experiments were attempted. Treatment of **18**, or the corresponding sulfoxide or sulfone, with various strong bases invariably produced highly colored solutions characteristic of benzylic anions of this type (for example, **19**; deep purple color at −78 °C). However, no sign of cyclized (tetracyclic) products was ever detected. Warming the anions under various conditions resulted in decomposition, generally associated with elimination of the sulfur substituent (thiophenoxide from **19**).

Since there was extensive precedent for cyclization by the related (and, presumably more robust) cyanide-stabilized anion **22**,[3,4] the sulfide **18** was converted into the cyanide **21** via a two-step process. First, the lithio sulfide **19** was generated with lithium diisopropylamide and converted into cyano sulfide **20** (71%) using *p*-toluenesulfonyl cyanide.[9] Desulfurization with Raney Ni in ethanol resulted in extensive cyanide reduction, but in the deactivating solvent acetonitrile, Raney Ni cleanly produced the desired **21** in 96% yield.

Cyclization of **21** occurred in 75% yield under somewhat modified Hassall conditions. The anion **22** was generated with potassium hexamethyldisilazide in dimethoxyethane containing 2–3% of 1,3-dimethyl-2-imidazolidinone as an "enhancer".[10] Heating at reflux under scrupulously oxygen-free conditions resulted in the gradual fading of the intensely purple **22**, and neutralization of the product afforded a mixture of unstable tautomers **23** and **24**. The products were oxidized with hydrogen peroxide + diisopropylethylamine in THF to the stable quinone **25** (84%). Finally, the ketal blocking group was removed by transketalization in acetone + triflic acid catalyst. This reaction gave the *O*-silyl-protected anthracyclinone in 84% yield. Under similar conditions reported by Krohn et al. (acetone + BF_3·Et_2O),[11] the yield of **26** was somewhat lower due to partial cleavage of the *O*-silyl ether to the benzylic (C_7) alcohol.

Since this work was initiated, other groups have reported on the difficulty of adding organometallic nucleophiles to the C_9 ketone of various anthracyclinones.[11,12] We have not addressed this issue in detail, but the combination of acidic benzylic protons in **26** together with the presence of anthraquinone carbonyl groups (and only one stabilizing phenolic ether oxygen group) has so far prevented a

(8) Middleton, W. J. *Org. Synth.* **1985**, *64*, 221–225.

(9) Kahne, D.; Collum, D. B *Tetrahedron Lett.* **1981**, *22*, 5011–5014.
(10) For a discussion of urea-type solvents, see: Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.
(11) Krohn, K.; Tolkiehn, K. *Chem. Ber.* **1979**, *112*, 3453–3471.
(12) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Lett.* **1984**, 1543–1546.

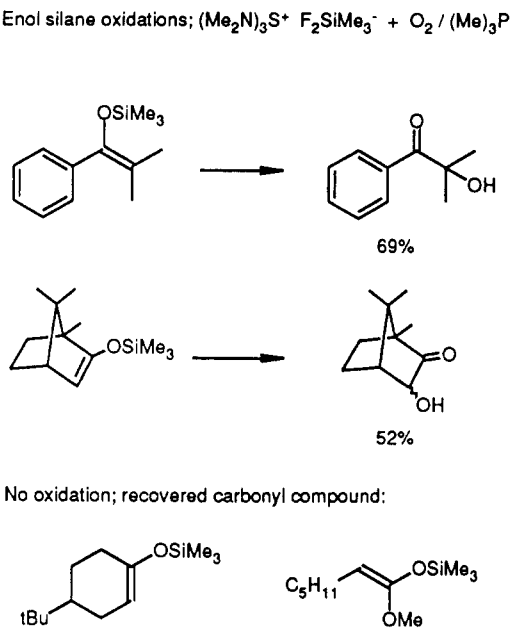

Figure 4.

practical conversion to tertiary alcohols such as **28**. The desired product could not be detected by using $EtCeCl_2$,[13] and various titanium reagents were not promising.[14] A modified zirconium reagent based on precedents by Seebach et al.[15] and corresponding to the stoichiometry of $Et_3Zr-OC_3H_7$ was especially promising in model compounds such as $PhCH_2COCH_2Ph$ and did give a reasonably clean mixture of carbonyl adducts with **26**. This mixture (containing **27** as well as the desired C_9 ketone adduct) could not be purified. However, cleavage of the silyl ether with Bu_4N^+F/THF destroyed **27**, presumably via aromatization of ring A, and allowed the isolation of a partially characterized product having spectral properties consistent with the desired **28** in low yield. Further efforts in this direction using the Hassall cyclization strategy will need to convert the ketal into a tertiary carbinol at a much earlier stage of synthesis.

The exceptionally efficient oxidation of benzylic silane **15** into the alcohol **17** prompted some effort to probe the generality of this process. Regardless of mechanistic interpretation, the extrapolation to simple enol silanes is obvious, and in certain cases the oxidation does succeed. Figure 4 summarizes the successful examples found after a substantial effort. More significant than the two cases that worked are the many examples that did not. As indicated at the bottom of Figure 4, typical enol silanes derived from cyclohexanones or unbranched esters are simply cleaved to the parent carbonyl compound despite excruciating care to maintain anhydrous conditions, and using the same solvents and reagents that allow oxidation of **15** in 95% yield in parallel experiments. We are convinced that these contradictory results are not accidental and that they reflect the ability of TASF to act as a kinetically effective proton donor toward enolates. This would have to involve anion-induced fragmentation of $CH_3N(Me)S^+(NMe_2)_2$ to $CH_2{=}NMe$ if the protons are derived from TASF itself. In any event, the astonishing difference between **15** and the simple enol silanes of Figure 4 would then have to be attributed to kinetic factors. The rate of oxygenation vs anion protonation appears to be decisive, but it bears no simple relationship to anion stability. Thus, even $PhCH_2SiMe_3$ is converted in measurable (20% by internal standard NMR technique) yield into alcohol ($PhCH_2OH$) under the same conditions that result in protodesilylation of simple enol silanes in Figure 4. In view of this experience, it is fortunate that **15** was studied first. The transformation to **17** is eminently practical and allows use of the concept of Garland et al. (benzylic silicon as latent C_7 hydroxyl) without the restriction to phenolic anthracyclinones.[7,16,17]

Experimental Section

Melting points are uncorrected (hot-stage microscope apparatus). HPLC separations were done by using a Laboratory Data Control Constametric II pump, Whatman Partisil Magnum 9 preparative column, and Waters Associates differential refractometer R401. Analytical TLC was performed on EM Science precoated TLC plates with silica gel F-254. Product purity is estimated at ≥95% by ^1H NMR unless stated otherwise.

Diethyl ether and tetrahydrofuran (THF) were dried over sodium–benzophenone and were distilled freshly prior to use. Dry chloroform, methylene chloride, and toluene were obtained by distillation from calcium hydride.

Ethynyl 2,3-Dimethoxyphenyl Ketone (10). Into a 250-mL three-necked flask equipped with mechanical stirrer and addition funnel was placed a solution of 3-(2,3-dimethoxyphenyl)-1-propyn-3-ol[4] (0.519 g, 2.70 mmol) in 35 mL of a 1:4 mixture of ether–methylene chloride. The alcohol solution was cooled to 0 °C. Excess Jones reagent[18] was likewise chilled. The Jones reagent was dripped into the vigorously stirred reaction mixture at a moderate rate until TLC indicated all starting material had disappeared (30 min, 75 mL of Jones reagent, 49.5 mmol). The layers were then separated and the aqueous phase was extracted with 1:4 ether–methylene chloride (1 × 20 mL). Combined organic phases were washed with saturated $NaHCO_3$ (3 × 25 mL), dried ($MgSO_4$), filtered, and evaporated (aspirator) to afford crude product (0.398 g, 2.09 mmol, 78%) as a yellow oil, pure by 200-MHz NMR. The product could be crystallized from ethyl acetate/hexane to give light yellow crystals of **10** (2 crops, 0.363 g, 71%), mp 51–52 °C (lit.[4] mp 51–52 °C).

4-Cyano-1-(trimethylsiloxy)-3-(trimethylsilyl)-1,4-cyclohexadiene (1). To a solution of propiolonitrile[19] (0.169 g, 3.32 mmol) in cyclohexane (2.0 mL) was added 1-(trimethylsilyl)-3-(trimethylsilyoxy)-1,3-butadiene[20] (0.518 g, 2.71 mmol) and the reaction mixture was divided evenly between two 15 cm × 7 mm diameter Pyrex tubes previously washed with acetone (3×), pH 7 buffer (3×), and distilled water (5×), flame-dried, and cooled under N_2. The reaction tubes were chilled to −78 °C under N_2, sealed, and then heated to 67 ± 2 °C for 70 h. Evaporation of solvent and unreacted starting materials (0.05 mmHg, 25 °C) gave **1** as an oil, pure by NMR (0.608 g, 85%): TLC silica gel 60, 5% EtOAc/hexane, R_f 0.38; MS, m/e base 176; exact mass for $C_{13}H_{23}ONSi_2$ 265.1312, found 265.1318; error 2.3 ppm; IR (neat, cm^{-1}) CN, 2240; 200-MHz NMR ($CDCl_3$, ppm) 6.41 (1 H, t, J = 3.5 Hz), 4.81 (1 H, d, J = 4.8 Hz), 2.85–2.78 (2 H, m), 2.49–2.46 (1 H, m), 0.20 (9 H, s), 0.13 (9 H, s).

Ketal 2. Adduct **1** (0.649 g, 2.44 mmol), 2,2-dimethyl-

(13) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233–4236. (b) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904–3912.

(14) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1–54.

(15) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31–45. Weidmann, B.; Maycock, C. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1552–1557.

(16) It should be noted that related oxidation conditions in the presence of strong base have been used to introduce oxygen C_7 in more highly activated anthracyclines having no benzylic silicon: Tanaka, H.; Yoshioka, T.; Shimauchi, Y.; Yoshimoto, A.; Ishikura, T. *Tetrahedron Lett.* **1984**, *25*, 3355–3358. Coburn, C. E.; Anderson, D. K.; Swenton, J. S. *J. Org. Chem.* **1983**, *48*, 1455–1461.

(17) For introduction of C_7 oxygen via bromination/solvolysis, see: Wong, C. M.; Schwenk, R.; Popien, D.; Ho, T.-L. *Can. J. Chem.* **1973**, *51*, 466–467.

(18) Brown, H. C.; Garg, C. P.; Liu, K.-T. *J. Org. Chem.* **1971**, *36*, 387–390.

(19) Miller, F. A.; Lemmon, D. H. *Spectrochimica Acta* **1967**, *23A*, 1415.

(20) Reid, J. G., Ph.D. Dissertation, 1983, University of Wisconsin, Madison, WI.

propane-1,3-diol (Aldrich, recrystallized from toluene; 1.28 g, 12.2 mmol), camphorsulfonic acid (Aldrich, recrystallized from ethyl acetate; 0.016 g, 0.076 mmol), and THF (2.5 mL) were placed into a dry flask fitted with a magnetic stirrer. The reaction vessel was swept with nitrogen for 10 min, sealed (Parafilm), and stirred for 9 days at room temperature. The reaction mixture was then diluted with ether (25 mL), washed with saturated $NaHCO_3$ (1 × 10 mL), water (4 × 10 mL), and saturated NaCl (1 × 10 mL), dried ($MgSO_4$), and filtered, and solvent was evaporated to afford ketal **2** as an oil (0.599 g, 88%), sufficiently pure for the next step: analytical TLC, silica gel 60, 20% EtOAc/hexane, R_f 0.47; MS, m/e base 128; exact mass for $C_{15}H_{25}O_2NSi$ 279.1648, found 279.1656; error 2.8 ppm; IR (neat, cm^{-1}) CN, 2230; 200-MHz NMR ($CDCl_3$, ppm) 6.39 (1 H, m), 3.53 (2 H, s), 3.47 (2 H, AB q, J = 11.5 Hz), 2.73 (1 H, ddt, J = 19.0, 5.6, 2.6 Hz), 2.31 (1 H, dt, J = 19.0, 3.3 Hz), 2.23 (1 H, ddd, J = 13.4, 6.0, 2.6 Hz), 2.00–1.87 (1 H, m), 1.49 (1 H, dd, J = 13.4, 10.6 Hz), 1.02 (3 H, s), 0.93 (3 H, s), 0.17 (9 H, s).

Dibal Reduction of Nitrile 2 to Aldehyde 3. To a −78 °C solution of nitrile **2** (0.960 g, 3.44 mmol) in CH_2Cl_2 (2.5 mL) under N_2 was added diisobutylaluminum hydride (Dibal; Aldrich, 0.85 M in hexane; 5.40 mL, 4.59 mmol) dropwise over 5 min. After 5 h excess Dibal was destroyed by addition of ethanol (2 mL) at −78 °C. The orange solution was diluted with ether (20 mL) and poured into a mixture of EtOAc (20 mL) and saturated NH_4Cl (20 mL). After mixing thoroughly, the biphasic solution was filtered through Celite to remove gelatinous aluminum salts and the layers were separated. The aqueous phase was extracted with EtOAc (1 × 20 mL), and the combined organic phases were washed with saturated NaCl (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). Chromatography afforded pure aldehyde **3** (0.84 g, 86%) as an oil: TLC silica gel 60, 20% EtOAc/hexane, R_f 0.47; MS, m/e base 139; exact mass for $C_{15}H_{26}O_3Si$ 282.1644, found 282.1614; error 10.6 ppm; IR (neat, cm^{-1}) CH=O, 1685; 200-MHz NMR ($CDCl_3$, ppm) 9.35 (1 H, s), 6.49 (1 H, br t, J = 3.5 Hz), 3.47 (2 H, s), 3.45 (2 H, AB q, J = 6.2 Hz), 2.74 (1 H, dt, J = 19.1, 3.5 Hz), 2.55 (1 H, dtd, J = 19.1, 4.9, 2.2 Hz), 2.21–2.06 (2 H, m), 1.78–1.64 (1 H, m), 1.01 (3 H, s), 0.86 (3 H, s), −0.01 (9 H, s).

Horner–Emmons–Wadsworth Olefination of Aldehyde 3: Preparation of Diene Ester 4. To a THF (2 mL) slurry of NaH (Alfa, 50% in mineral oil; 0.051 g, 1.06 mmol) previously washed with hexane (2 × 2 mL) was cautiously added triethyl phosphonoacetate (Aldrich; 0.17 mL, 0.192 g, 0.86 mmol) dropwise under nitrogen. The anion was allowed to form over 30 min. A solution of aldehyde **3** (0.232 g, 0.082 mmol) in THF (4 mL) was then added. The reaction mixture was stirred at room temperature for 5.5 h under nitrogen before diluting with EtOAc (10 mL) and washing with saturated NaCl (2 × 5 mL). The crude product solution was dried ($MgSO_4$), filtered, and concentrated (aspirator). Purification by column chromatography afforded diene ester **4** (0.27 g, 94%): oil; TLC silica gel 60, 20% EtOAc/hexane, R_f 0.53; MS, m/e base 158; exact mass for $C_{19}H_{32}O_4Si$ 352.2061, found 352.2071; error 2.9 ppm; IR (neat, cm^{-1}) C=O, 1710; 200-MHz NMR ($CDCl_3$, ppm) 7.24 (1 H, d, J = 15.8 Hz), 5.88 (1 H, t, J = 4.5 Hz), 5.79 (1 H, d, J = 15.8 Hz), 4.19 (2 H, q, J = 7.1 Hz), 3.56 (2 H, dd, J = 11.5, 4.3 Hz), 3.42 (2 H, ddd, J = 11.5, 8.7, 1.6 Hz), 2.64 (1 H, br d, J = 18.1 Hz), 2.47 (1 H, br dd, J = 18.1, 5.2 Hz), 2.20–2.05 (2 H, m), 1.93–1.82 (1 H, m), 1.28 (3 H, t, J = 7.1 Hz), 1.08 (3 H, s), 0.86 (3 H, s), 0.02 (9 H, s).

Reduction of Diene Ester 4 to Diene Alcohol 5. To a −78 °C solution of ester **4** (0.274 g, 0.777 mmol) in CH_2Cl_2 (10 mL) under nitrogen was added dropwise diisobutylaluminum hydride (Dibal, Aldrich; 1 M in hexane, 1.7 mL, 1.7 mmol) over several minutes. After stirring for 1.5 h at −78 °C, excess Dibal was quenched with ethanol (0.25 mL). The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 10% aqueous H_2SO_4 (2 × 10 mL), saturated $NaHCO_3$ (1 × 10 mL), and saturated NaCl (1 × 10 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). Chromatography of the residual oil afforded diene alcohol **5** (0.24 g, 99%) which could be crystallized as colorless cubes: solid, mp 83–85 °C (crystallized from hexane); MS, m/e base 128; exact mass for $C_{17}H_{30}O_3Si$ 310.1956, found 310.1963; error 2.3 ppm; IR (neat, cm^{-1}) OH, 3410; 200-MHz NMR ($CDCl_3$, ppm) 6.13 (1 H, d, J = 15.6 Hz), 5.73 (1 H, dt, J = 15.6, 5.8 Hz), 5.52 (1 H, t, J = 4.3 Hz), 4.16 (2 H, d, J = 5.8 Hz), 3.57 (2 H, dd, J = 11.5, 2.4 Hz), 3.42 (2 H, ddd, J = 11.5, 7.5, 1.6 Hz), 2.55 (1 H, br d, J = 18.0 Hz), 2.41 (1 H, br dd, J = 18.0, 4.9 Hz), 2.20–2.02 (2 H, m), 1.79 (1 H, dd, J = 11.9, 5.1 Hz), 1.33 (1 H, br s), 1.07 (3 H, s), 0.86 (3 H, s), 0.02 (9 H, s).

Acetylation of Diene Alcohol 5: Preparation of Acetate 6. To a solution of alcohol **5** (0.039 g, 0.125 mmol) in THF (2.0 mL) were added triethylamine (Aldrich, distilled from P_2O_5; 0.035 mL, 0.025 g, 0.25 mmol), acetic anhydride (Mallinckrodt, distilled; 0.027 g, 0.26 mmol), and (dimethylamino)pyridine (Dmap, Aldrich; 0.007 g, 0.06 mmol). The reaction mixture was stirred under N_2 for 15 h. After concentration (aspirator), the crude product was purified by column chromatography to afford acetate **6** (0.043 g, 98%): oil; TLC silica gel 60, 20% EtOAc/hexane, R_f 0.53; MS, m/e base 126; exact mass for $C_{19}H_{32}O_4Si$ 352.2061, found 352.2071; error 2.9 ppm; IR (neat, cm^{-1}) CO_2, 1740; 200-MHz NMR ($CDCl_3$, ppm) 6.18 (1 H, d, J = 15.8 Hz), 5.64 (1 H, dt, J = 15.8, 6.5 Hz), 5.55 (1 H, br t, J = 4.4 Hz), 4.58 (2 H, d, J = 6.5 Hz), 3.60–3.37 (4 H, m), 2.60–2.30 (2 H, m), 2.20–2.00 (2 H, m), 2.05 (3 H, s), 1.79 (1 H, dd, J = 12.1, 5.5 Hz), 1.08 (3 H, s), 0.86 (3 H, s), 0.01 (9 H, s).

Preparation of Diene Sulfide 7. To a solution of tri-*n*-butylphosphine (Aldrich; 0.53 mL, 0.43 g, 2.13 mmol) in THF (2 mL) under N_2 was added a solution of *N*-(phenylsulfenyl)succinimide[6] in THF (4 mL). The dark blue-green solution was stirred for 20 min. Alcohol **5** (0.326 g, 1.05 mmol) dissolved in THF (9 mL) was added via cannula. After being stirred at room temperature for 1 h, the reaction mixture was diluted with EtOAc (50 mL), washed with 5% NaOH (3 × 20 mL) and saturated NaCl (1 × 20 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). The residual oil was purified by column chromatography to afford diene sulfide **7** (0.38 g, 89%) as an oil: TLC silica gel 60, 5% EtOAc/hexane, R_f 0.31; MS, m/e base 159; exact mass for $C_{23}H_{34}O_2SSi$ 402.204, found 402.2048; error 2 ppm; IR (neat, cm^{-1}) C—O, 1120; 200-MHz NMR ($CDCl_3$, ppm) 7.35–7.11 (5 H, m), 6.04 (1 H, d, J = 15.5 Hz), 5.63 (1 H, dt, J = 15.5, 7.2 Hz), 5.45 (1 H, t, J = 4.2 Hz), 3.60 (2 H, d, J = 7.2 Hz), 3.56 (2 H, d, J = 11.0 Hz), 3.40 (2 H, ddd, J = 11.4, 5.0, 1.7 Hz), 2.57 (1 H, br d, J = 18.1 Hz), 2.37 (1 H, br dd, J = 18.1, 4.6 Hz), 2.10 (1 H, ddd, J = 12.3, 6.7, 1.5 Hz), 2.01–1.95 (1 H, m), 1.79 (1 H, ddd, J = 12.3, 5.5, 1.0 Hz), 1.08 (3 H, s), 0.85 (3 H, s), −0.03 (9 H, s).

Diels–Alder Cycloaddition of Ynone 10 and Diene Sulfide 7: Aromatization of the Adducts. Preparation of Benzyl Sulfides 15 and 16. Ynone **10** (0.56 g, 2.95 mmol) and diene sulfide **7** (1.19 g, 2.96 mmol) were dissolved in toluene (3.0 mL), and the resultant solution was divided evenly between four 15 cm × 7 mm diameter Pyrex tubes previously washed with acetone (3×), pH 7 buffer (3×), and distilled water (5×), flame-dried, and cooled under nitrogen. The tubes were cooled to −78 °C under H_2 and then sealed. After heating at 134 ± 2 °C for 72 h, solvent was evaporated to afford crude Diels–Alder adducts as the mixture of diastereo- and regioisomers. The crude product was carried on to the aromatization step without further purification.

Crude Diels–Alder adducts from above were dissolved in dioxane (30 mL). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (Aldrich; 0.723 g, 3.19 mmol) was added and the blue-green reaction mixture was heated to 70 °C under N_2. After 15.5 h, the reaction was diluted with ether (50 mL), washed with 5% NaOH (5 × 30 mL) and saturated NaCl (1 × 30 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). The crude product mixture was then purified by preparative LC to afford the desired benzyl sulfide (**15**; 1.1 g, 65%) and the regioisomer **16**.

15: solid, mp 105–106 °C (crystallized from 10% EtOAc/hexane); MS, m/e base 165; exact mass for $C_{34}H_{42}O_5SSi$ 590.2512, found 590.2523; error 2 ppm; IR (neat, cm^{-1}) C=O, 1745; 200-MHz NMR ($CDCl_3$, ppm) 7.32–7.00 (10 H, m), 4.63 (1 H, d, J = 13.8 Hz), 4.36 (1 H, d, J = 18.8 Hz), 3.90 (3 H, s), 3.66 (3 H, s), 3.53 (2 H, AB q, J = 11.6 Hz), 3.37 (2 H, AB q, J = 11.3 Hz), 3.07 (1 H, dd, J = 16.3, 1.8 Hz), 2.79 (1 H, t, J = 8.3 Hz), 2.51 (1 H, t, J = 8.3 Hz), 2.29 (1 H, ddd, J = 13.5, 8.3, 1.8 Hz), 1.76 (1 H, dd, J = 13.5, 8.3 Hz), 1.04 (3 H, s), 0.85 (3 H, s), −0.05 (9 H, s).

16: oil; TLC silica gel HPLC M-9, 20% EtOAc/hexane, R_f 0.33; MS, m/e base 269; exact mass for $C_{34}H_{42}O_5SSi$ 590.2512, found 590.2528; error 2.8 ppm; IR ($CHCl_3$, cm^{-1}) C=O, 1670; 200-MHz NMR ($CDCl_3$, ppm) 7.54–7.00 (9 H, m), 6.95 (1 H, s), 3.99 (2 H, s), 3.88 (3 H, s), 3.68 (2 H, AB q, J = 9.7 Hz), 3.59 (1 H, d, J = 16.4 Hz), 3.42 (3 H, s), 3.39 (1 H, dd, J = 11.4, 1.8 Hz), 3.26 (1

H, br d, J = 11.4 Hz), 2.87 (1 H, d, J = 16.4 Hz), 2.61 (1 H, t, J = 8.1 Hz), 2.22 (1 H, ddd, J = 13.6, 8.1, 1.8 Hz), 1.88 (1 H, dd, J = 13.6, 8.2 Hz), 1.12 (3 H, s), 0.76 (3 H, s), −0.01 (9 H, s).

Oxidation of Benzyl Silane 15: Preparation of Benzyl Alcohol 17. Tris(dimethylamino)sulfonium difluorotrimethylsilicate[8] (0.11 g, 0.41 mmol) and trimethyl phosphite (Aldrich, distilled from sodium; 0.10 mL, 0.11 g, 0.85 mmol) were dissolved in acetonitrile (5 mL) under N_2 and cooled to −37 °C. The acetonitrile solution was saturated with oxygen passed sequentially through a −78 °C trap, Drierite/KOH tower, activated alumina, and P_2O_5 coated glass wool, bubbled below the surface for 15 min. A solution of benzyl silane **15** (0.090 g, 0.15 mmol), previously dried by azeotropic distillation of toluene at reduced pressure (5×), in acetonitrile (2 mL) was added in small portions via cannula over 15 min with continuous oxygen bubbling throughout. The reaction mixture was stirred for another 50 min and allowed to gradually warm to room temperature. The reaction was quenched with methanol (0.15 mL), diluted with EtOAc (30 mL), washed with saturated NH_4Cl (15 mL) and saturated NaCl (15 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). The crude product was purified by column chromatography to afford **17** (0.077 g, 95%): oil; TLC silica gel 60, 25% EtOAc/25% CH_2Cl_2/50% hexane, R_f 0.36; MS, m/e base 425; exact mass for $C_{31}H_{34}O_6S$ 534.2067, found 534.2074; error 1.4 ppm; IR (neat, cm^{-1}) OH, 3460, C=O, 1675; 200-MHz NMR ($CDCl_3$, ppm) 7.48 (1 H, s), 7.43–6.96 (9 H, m), 4.72 (1 H, br dt, J = 10.8, 4.6 Hz), 4.46 (2 H, AB q, J = 13.0 Hz), 3.91 (3 H, s), 3.69 (3 H, s), 3.55 (2 H, AB q, J = 11.5 Hz), 3.49 (2 H, s), 3.34 (1 H, br d, J = 16.9 Hz), 2.99 (1 H, d, J = 10.8 Hz), 2.77 (1 H, d, J = 16.9 Hz), 2.41 (1 H, ddd, J = 14.0, 4.1, 1.9 Hz), 2.19 (1 H, dd, J = 14.0, 5.1 Hz), 1.04 (3 H, s), 0.90 (3 H, s).

Protection of Alcohol 17: Preparation of *tert*-Butyldimethylsilyl Ether 18. To a solution of benzyl alcohol **17** (0.071 g, 0.13 mmol) in DMF was added imidazole (Aldrich; 0.034 g, 0.50 mmol) and *tert*-butyldimethylsilyl chloride (Petrarch; 0.041 g, 0.27 mmol). The reaction mixture was stirred under nitrogen at 33 °C for 24 h. The crude product solution was diluted with 1:1 ether–hexane (30 mL), washed with saturated NH_4Cl (2 × 15 mL) and water (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). Purification afforded silyl ether **18** (0.12 g, 92%) as an oil: TLC silica gel 60, 20% EtOAc/hexane, R_f 0.32; MS, m/e base 539; exact mass for $C_{37}H_{48}O_6SSi$ 648.2929, found 648.294; error 1.8 ppm; IR (neat, cm^{-1}) C=O, 1660; 200-MHz NMR ($CDCl_3$, ppm) 7.55 (1 H, s), 7.31–7.03 (8 H, m), 6.96 (1 H, dd, J = 6.5, 2.7 Hz), 4.81 (1 H, dd, J = 10.9, 6.1 Hz), 4.50 (2 H, AB q, J = 13.9 Hz), 3.90 (3 H, s), 3.69 (3 H, s), 3.54 (2.54 (2 H, AB q, J = 12.3 Hz), 3.46 (2 H, s), 3.17 (1 H, br d, J = 16.2 Hz), 2.82 (1 H, d, J = 16.2 Hz), 2.68 (1 H, ddd, J = 12.8, 6.1, 2.0 Hz), 1.78 (1 H, dd, J = 12.8, 10.9 Hz), 0.98 (3 H, s), 0.96 (3 H, s), 0.94 (9 H, s), 0.25 (6 H, s).

Preparation of Cyano Sulfide 20. To a −78 °C solution of sulfide **18** in THF (7 mL) was added lithium diisopropylamide (0.335 M in THF–hexane, 2.2 mL, 0.74 mmol) under N_2. The anion was allowed to form over 30 min. The deep purple anion solution was then added to a 0 °C solution of *p*-toluenesulfonyl cyanide[9] (TsCN; Aldrich, distilled and recrystallized from hexane; 0.33 g, 1.83 mmol) in THF (1 mL) via cannula while stirring rapidly. Residual anion solution was rinsed into the TsCN flask with THF (3 × 1 mL). When all purple color had faded (30 s), the reaction was quenched with saturated NH_4Cl, 5 mL) and extracted with EtOAc (20 mL). The organic solution was washed with saturated NaCl (15 mL). The combined aqueous phases were extracted with EtOAc (20 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated (aspirator). The resultant oil was purified to afford the desired cyano sulfide **20** (0.28 g, 71%) together with a dinitrile byproduct (0.023 g, 6%) and recovered starting sulfide (0.048 g, 13%).

20: oil; TLC silica gel HLC M-0, 20% EtOAc/hexane, R_f 0.25; MS, m/e base 236; exact mass for $C_{38}H_{47}O_6NSSi$ 673.2881, found 673.2864; error 2.6 ppm; IR (neat, cm^{-1}) CN, 2275, C=O, 1670; 200-MHz NMR ($CDCl_3$, ppm) 7.72 (0.5 H, s), 7.56–6.96 (9.5 H, m), 6.48 (0.5 H, s), 6.43 (0.5 H, s), 4.82 (0.5 H, dd, J = 10.5, 4.9 Hz), 4.69 (0.5 H, dd, J = 9.7, 5.0 Hz), 3.93 (1.5 H, s), 3.92 (1.5 H, s), 3.75 (1.5 H, s), 3.74 (1.5 H, s), 3.59–3.38 (4 H, m), 3.17 (1 H, br d, J = 17.2 Hz), 2.90–2.67 (2 H, m), 1.84–1.68 (1 H, m), 1.03 (1.5 H, s), 1.01 (1.5 H, s), 0.97 (4.5 H, s), 0.96 (3 H, s), 0.94 (4.5 H, s), 0.23 (1.5 H, s), 0.18 (1.5 H, s), 0.14 (3 H, s).

Dinitrile: oil; TLC silica gel HPLC M-9, 20% EtOAc/hexane, R_f 0.19; IR ($CHCl_3$, cm^{-1} CN, 2240, C=O, 1670; 200-MHz NMR ($CDCl_3$, ppm) 8.71 (1 H, s), 7.59 (1 H, s), 7.36–6.90 (8 H, m), 5.00–4.93 (1 H, m), 3.97 (3 H, s), 3.62 (3 H, s), 3.56–3.48 (4 H, m), 3.21 (2 H, AB q, J = 16.9 Hz), 2.78–2.71 (1 H, m), 1.85 (1 H, br dd, J = 25.0, 11.0 Hz), 1.01 (3 H, s), 0.95 (12 H, s), 0.15 (6 H, s).

Raney Nickel Reduction of Cyano Sulfide 20: Preparation of Nitrile 21. Cyano sulfide **20** (0.144 g, 0.21 mmol) was dissolved in acetonitrile (7 mL) and W-2 Raney nickel alloy[21] (ca. 0.10 g) was added. The reaction mixture was heated to reflux under N_2 for 66.5 h with vigorous stirring. Filtration of the crude reaction mixture through Celite, solvent evaporation (aspirator), and purification of the resultant oil by column chromatography gave nitrile **21** (0.12 g, 95%) as an oil: TLC silica gel 60 25% EtOAc/25% CH_2Cl_2/50% hexane, R_f 0.71; MS, m/e base 422; exact mass for $C_{32}H_{43}O_6NSi$ 565.2849, found 565.2848, error 0.1 ppm; IR (neat, cm^{-1}) CN, 2140, C=O, 1680; 200-MHz NMR ($CDCl_3$, ppm) 7.76 (1 H, s), 7.16 (1 H, s), 7.13–7.04 (2 H, m), 6.91 (1 H, dd, J = 7.0, 2.2 Hz), 4.90 (1 H, dd, J = 10.9, 5.9 Hz), 4.20 (2 H, AB q, J = 19.5 Hz), 3.91 (3 H, s), 3.67 (3 H, s), 3.55 (2 H, AB q, J = 11.4 Hz), 3.46 (2 H, AB q, J = 11.3 Hz), 3.17 (1 H, br d, J = 16.5 Hz), 2.83 (1 H, d, J = 16.5 Hz), 2.74 (1 H, ddd, J = 12.8 5.9, 2.0 Hz), 1.80 (1 H, dd, J = 12.8, 10.9 Hz), 1.01 (9 H, s), 0.99 (3 H, s), 0.96 (3 H, s), 0.30 (3 H, s), 0.22 (3 H, s).

Cyclization of Nitrile 21: Preparation of Tetracycle 23. Nitrile **21** (0.046 g, 0.81 mmol) was dried by azeotropic distillation of toluene at reduced pressure (2×) and the reaction flash was then fitted with a reflux condenser and purged with N_2 for 15 h. The nitrile was dissolved in glyme (10 mL). 1,3-Dimethyl-2-imidazolidinone (Aldrich; stirred over NaH, filtered and distilled at reduced pressure; 0.20 mL, 0.209 g, 1.83 mmol) and potassium bis(trimethylsilyl)amide[21] (0.336 M in THF, 0.24 mL, 0.081 mmol) were added sequentially. The deep purple anion solution was placed into a preheated 97 °C oil bath and the reaction was stirred at reflux under N_2. After 7.5 h the olive green reaction mixture was cooled to room temperature under N_2, quenched with saturated NH_4Cl (5 mL), and extracted with EtOAc (25 mL). The organic solution was washed with 2 M aqueous HCl (2 × 15 mL) and saturated NaCl (15 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). Purification by column chromatography (silica gel 60, 25% EtOAc/25% CH_2Cl_2/50% hexane, R_f 0.53) gave a dark yellow oil (0.032 g, 75%). NMR (200-MHz, $CDCl_3$) showed the product to be a mixture of anthrol **24** and diastereomeric anthrone **23** tautomers: MS, m/e base 390; exact mass for $C_{31}H_{39}NO_5Si$ 533.2587, found 533.2594; error 1.4 ppm; IR (neat, cm^{-1} OH, 3350, CN, 2220, C=O, 1650.

Oxidation of Cyclization Product 23 + 24: Preparation of Anthracyclinone 25. Cyclized nitrile **23** (0.037 g, 0.068 mmol) was dissolved in THF (5 mL) and hydrogen peroxide (Mallinckrodt; 30% in water, 2.0 mL, 17 mmol) was added. Upon addition of diisopropylethylamine (Aldrich; 0.25 mL, 0.186 g, 1.44 mmol) the yellow nitrile solution turned orange. After stirring for 36 h at room temperature, the bright yellow reaction mixture was diluted with EtOAc (30 mL), washed with saturated Na_2CO_3 (2 × 20 mL) and saturated NaCl (20 mL), then dried ($MgSO_4$), filtered, and concentrated (aspirator). Purification by column chromatography gave anthraquinone **25** (0.30 g, 84%) as an oil: TLC silica gel 60, 25% EtOAc/25% CH_2Cl_2/50% hexane, R_f 0.75; MS, m/e base 379; exact mass for $C_{30}H_{38}O_6Si$ 522.2427, found 522.2437; error 2 ppm; IR (neat, cm^{-1}) C=O, 1690; 200-MHz NMR ($CDCl_3$, ppm) 8.41 (1 H, s), 7.97 (1 H, d, J = 8.0 Hz), 7.95 (1 H, s), 7.71 (1 H, t, J = 8.2 Hz), 7.35 (1 H, d, J = 8.4 Hz), 4.97 (1 H, dd, J = 10.9, 6.3 Hz), 4.06 (3 H, s), 3.61 (2 H, AB q, J = 11.6 Hz), 3.52 (2 H, s), 3.42 (1 H, br d, J = 16.8 Hz), 3.09 (1 H, d, J = 16.8 Hz), 2.79 (1 H, ddd, J = 12.8, 6.3, 2.3 Hz), 1.89 (1 H, dd, J = 12.8, 10.9 Hz), 1.05 (3 H, s), 1.02 (9 H, s), 0.98 (3 H, s), 0.31 (3 H, s), 0.23 (3 H, s).

Deprotection of Anthraquinone 25: Preparation of Ketone 26. To a solution of anthraquinone **25** (0.017 g, 0.032 mmol) in acetone (distilled from K_2CO_3, 2 mL) was added trifluoromethanesulfonic acid solution (3 M; 0.0113 M in acetone, 0.40 mL, 0.0045 mmol). After stirring under N_2 for 7.5 h at room

(21) Mozingo, R. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, pp 181–183.

temperature, the reaction was quenched with pH 7 buffer (Aldrich; 2 mL) and extracted with EtOAc (15 mL). The organic solution was washed with saturated NaCl (2 × 5 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). Purification by column chromatography gave ketone **26** (0.12 g, 84%): TLC oil, silica gel 60, 1:1:2 EtOAc/CH_2Cl_2/hexane, R_f 0.56; MS, *m/e*, no parent, $M - t\text{-}C_4H_9$; exact mass calcd for $C_{21}H_{19}O_5Si$ 379.1002, found 379.1042; error 10.5 ppm; IR (neat, cm^{-1}) C=COH, 3440; C=O, 1730, C=O, 1685; 200-MHz NMR ($CDCl_3$, ppm) 8.29 (1 H, s), 8.03 (1 H, s), 7.98 (1 H, dd, J = 7.7, 1.1 Hz), 7.75 (1 H, t, J = 8.0 Hz), 7.37 (1 H, dd, J = 8.2, 1.1 Hz), 5.21 (1 H, t, J = 4.7 Hz), 4.08 (3 H, s), 3.80 (2 H, AB q, J = 20.4 Hz), 2.76 (1 H, d, J = 5.2 Hz), 2.75 (1 H, d, J = 4.1 Hz), 0.87 (9 H, s), 0.17 (3 H, s), 0.02 (3 H, s).

Anthracyclinone 28. A stock solution of trichlorozirconium *n*-propoxide was prepared by dissolving $ZrCl_4$ (Fluka; 10.143 g, 43.53 mmol) in glyme (25 mL) with ice bath cooling under N_2 and then adding a slution of zirconium tetra-*n*-propoxide (Fluka: 4.5 mL, 4.76 g, 14.53 mmol) in glyme (20 mL). The solution was brought up to 57-mL volume with additional glyme and then stirred overnight under N_2. The resultant grey-brown solution was used without further manipulation as 1 M trichlorozirconium *n*-propoxide.

Triethylzirconium *n*-propoxide was prepared in situ by addition of ethyllithium[23] (1.35 M in ether, 0.25 mL, 0.34 mmol) to a 0 °C solution of trichlorozirconium *n*-propoxide (see above; 1 M in glyme, 1.2 mL, 1.2 mmol) diluted with glyme (1 mL) under N_2. After stirring for 30 min, a 0 °C solution of ketone **26** (0.0057 g, 0.013 mmol) in glyme (1 mL) was added dropwise via cannula followed by an additional portion of glyme (1 mL). After 1 h the reaction mixture was allowed to gradually warm to room temperature. The reaction mixture was quenched after a total reaction time of 15 h by being poured into saturated NH_4Cl (3 mL). The resultant suspension was extracted with EtOAc (5 mL) and the organic phase was then washed with saturated NaCl (2 × 3 mL), dried ($MgSO_4$), filtered, and concentrated (aspirator). Preparative TLC (25% EtOAc/25% CH_2Cl_2/50% hexane) on an analytical plate gave the desired quinone addition product **27** together with recovered ketone **26** (2:1:1 ratio by 200-MHz NMR spectroscopy, R_f 0.47, 0.005 g).

The inseparable product mixture from above was dissolved in THF (0.5 mL) and cooled to 0 °C under N_2. Tetrabutylammonium fluoride (Aldrich; 1 M in THF, 0.10 mL, 0.10 mmol) was then added and the cold bath was removed after being stirred for 5 min. The reaction was quenched after 7 h at room temperature by addition of saturated NH_4Cl (2 mL). Product was extracted with EtOAc (5 mL), and the organic phase was washed with saturated NaCl (3 mL), dried ($MgSO_4$), filtered, and concentrated to an oil (aspirator). Thin layer chromatography gave a fraction (ca. 0.001 g, R_f 0.43, 1:1 EtOAc/hexane) that contained characteristic anthraquinone signals in the aromatic region and other signals corresponding to the desired **28**, but crystalline material could not be obtained: MS, *m/e* no parent ion; M + 1, calcd for $C_{21}H_{21}O_5$ 353.1389, found 353.1361, error 8.0 ppm; 200-MHz NMR ($CDCl_3$, ppm) 8.33 (1 H, s), 7.97 (1 H, s), 7.95 (1 H, d, J = 7.7 Hz), 7.72 (1 H, t, J = 7.7 Hz), 7.35 (1 H, d, J = 7.7 Hz), 5.05–4.90 (1 H, m), 4.05 (3 H, s), 2.99 (2 H, AB q, J = 17.8 Hz), 2.34 (1 H, br d, J = 14.6 Hz), 2.26 (1 H, br s), 1.96 (1 H, dd, J = 14.6, 4.8 Hz), 1.72 (2 H, q, J = 7.5 Hz), 1.60 (1 H, br s), 1.06 (3 H, t, J = 7.5 Hz).

Oxidation of Trimethyl[(1-phenyl-2-methylprop-1-en-1-yl)oxy]silane. Triphenylphosphine (0.107 g, 0.408 mmol) and TASF[8] (0.114 g, 0.414 mmol) were partially dissolved in THF (5 mL) and cooled to 0 °C with stirring under N_2. To the phosphine/TASF mixture was rapidly added a solution of trimethyl[(1-phenyl-2-methylprop-1-en-1-yl)oxy]silane[24] in dry THF (4 mL) via cannula under N_2. Dry oxygen was then bubbled below the surface of the solution, exhaust gases were diluted with nitrogen, and the reaction mixture was maintained between 0 and 5 °C. After 2 h the reaction was quenched with saturated NH_4Cl (5 mL) and the product was extracted with 1:1 EtOAc–ether (15 mL), washed with saturated NH_4Cl (5 mL) and saturated NaCl (2 × 5 mL), dried ($MgSO_4$), filtered, and evaporated (aspirator). Purification by column chromatography gave α-hydroxybutyrophenone (0.036 g, 69%), identical by NMR comparison with authentic material.

Trimethyl[(1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)oxy]silane (Camphor Enol Trimethylsilyl Ether). Camphor (Eastman; 1.054 g, 6.926 mmol) was dissolved in THF (5 mL) and chilled to −78 °C under N_2. LDA (0.74 M in THF–hexane, 10.7 mL, 7.92 mmol)[25b] was added dropwise with stirring at −78 °C and the anion was allowed to form over 15 min. To the cold anion solution was added freshly distilled TMSCl (0.96 mL, 0.822 g, 7.57 mmol) with stirring. After 5 min the cold bath was removed and the reaction mixture was allowed to warm to ambient temperature over 2 h. The reaction mixture was then evaporated (25 mmHg, 20 °C), redissolved in pentane, filtered through Celite, and evaporated. The title enol silane was obtained after purification by rapid filtration column chromatography over silica gel (1.38 g, 89%) as an oil (5% EtOAc/hexane, R_f 0.35), purity ≥95% according to ^1H NMR comparison with literature data[26] of material prepared from α-bromocamphor.

***exo*- and *endo*-4-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (Oxidation of Camphor Enol Trimethylsilyl Ether).** Triphenylphosphine (0.102 g, 0.388 mmol) and TASF[8] (0.096 g, 0.349 mmol) were mixed in THF (5 mL) and then chilled to 0 °C under N_2. A solution of camphor enol silane (0.062 g) in THF (4 mL) was added rapidly via syringe. Immediately after the silane addition, dry oxygen was bubbled below the surface of the reaction with stirring and exhaust gases were diluted with nitrogen. After 5 h at 0–5 °C, the reaction was quenched with water (5 mL) and extracted with EtOAc (15 mL). The organic phase was washed with saturated NH_4Cl (1 × 5 mL) and saturated NaCl (2 × 5 mL), then dried ($MgSO_4$), filtered, and evaporated (25 mmHg, 20 °C). Column chromatography (25% EtOAc/25% CH_2Cl_2/50% hexane) afforded the title compound as a 1:1 mixture of epimers according to NMR comparison with literature data.[25b]

Oxidation of Benzyltrimethylsilane. Triphenylphosphine (0.222 g, 0.806 mmol) and TASF[8] (0.221 g, 0.80 mmol) were mixed in THF (5 mL) and the stirred suspension was chilled to −37 °C. Dry oxygen was bubbled below the surface of the TASF–phosphine mixture for 10 min and the exhaust gases were diluted with nitrogen. A solution of benzyltrimethylsilane (Petrarch; 0.113 g, 0.69 mmol) and 2,3-dimethylnaphthalene (NMR reference; Aldrich; 0.020 g, 0.128 mmol) in THF (2 mL) was added in small portions over 20 min while maintaining continuous oxygen bubbling at −37 °C. The reaction mixture was stirred an additional 5 min after the addition was completed and then was allowed to warm to room temperature over 30 min. Oxygen bubbling was stopped and the reaction was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (10 mL). The organic phase was washed with saturated NaCl (10 mL), dried ($MgSO_4$), filtered, and evaporated (100 mmHg, −5 °C). Conversion to benzyl alcohol was estimated at 20% by internal reference comparison.

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Registry No. 1, 113132-91-5; 2, 113132-92-6; 3, 113132-93-7; 4, 113132-94-8; 5, 113132-95-9; 6, 113132-96-0; 7, 113132-97-1; 9, 78725-65-2; 10, 78725-35-6; 15, 113132-98-2; 16, 113132-99-3; 17, 113133-00-9; 18, 113133-01-0; 18 dinitrile, 113133-02-1; 20, 113133-03-2; 21, 113133-04-3; 23, 113133-05-4; 24, 113133-06-5; 25, 113133-07-6; 26, 113133-08-7; 27, 113133-09-8; 28, 113133-10-1; propiolonitrile, 1070-71-9; 1-(trimethylsilyl)-3-(trimethylsiloxy)-1,3-butadiene, 67201-11-0; 2,2-dimethyl-1,3-propanediol, 126-30-7; trichlorozirconium *n*-propoxide, 113133-11-2; zirconium tetra-*n*-propoxide, 23519-77-9; [(1-phenyl-2-methylprop-1-en-1-yl)oxy]silane, 39158-85-5; camphor enol trimethylsilyl ether, 56613-17-3; *exo*-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, 22759-33-7; benzyltrimethylsilane, 770-09-2; α-hydroxybutyrophenone, 7473-98-5; camphor, 76-22-2; *endo*-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, 21488-68-6; benzyl alcohol, 100-51-6; triethylzirconium *n*-propoxide, 113133-12-3.

(22) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913–3918.
(23) Jones, R. G.; Gilman, H. *Org. React.* (*N.Y.*) **1951**, *6*, 339–366.
(24) Rubottom, G. M.; Lopez Nieves, M. I., *Tetrahedron Lett.* **1972**, *13*, 2423.
(25) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (b) Vedejs, E.; Larsen, S. *Org. Synth.* **1985**, *64*, 127.
(26) Joshi, G. C.; Pande, L. M. *Synthesis* **1975**, 450.