Annelation Reactions of Quinone Monoketals. Studies Directed at an Efficient Synthesis of Anthracyclinones

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The annelation chemistry of quinone monoketals with dimethyl homophthalate, 7-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone, and 7-methoxy-3-cyano-1(3*H*)-isobenzofuranone has been studied. The first two reagents mentioned above allowed the formation of oxygenated tri- and tetracyclic anthrone and anthraquinone systems in 40–50% yields. While less extensively studied, the 7-methoxy-3-cyano-1(3*H*)-isobenzofuranone afforded a 75% yield in an annelation reaction with a highly functionalized monoketal. These reactions, coupled with the unique effect of an allylic methoxyl group on the regiochemistry of quinone bisketal hydrolysis, allowed a regiospecific preparation of certain tetracyclic anthraquinones. The work reported herein comprises a formal synthesis of racemic daunomycinone and forms a basis for an efficient, practical synthesis of fully functionalized anthracyclinones.

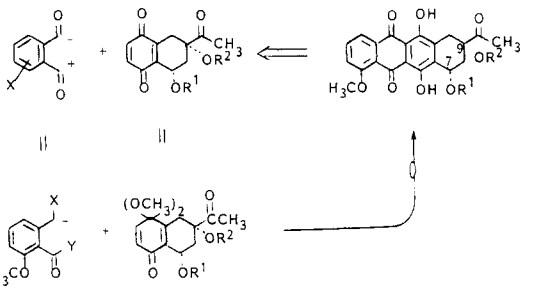
Introduction

Synthetic routes to anthracyclinone aglycons, specifically daunomycinone and adriamycinone, have attracted much attention.[1] We have been interested in convergent approaches for construction of tetracyclic anthraquinone systems under mild conditions.[1a,2] A strategy that appeared promising in achieving these objectives is outlined in Scheme I. A quinone monoketal would act as a regiospecific quinone equivalent while a second species would serve as a 1,4-dipole synthon.[3] We report herein conditions and reagents that lead to construction of anthraquinone systems via the strategy outlined in Scheme I.

The 1,4-Dipole Synthon

A number of reagents (Table I) could function as the required 1,4-dipole synthon;[4-8] of course, several of these would require subsequent oxidation of the product to the quinone oxidation state. The Schmid system[4] was studied first since 1 was readily available from the commercial diacid, and a convenient synthesis of the 3-methoxyl derivative was reported.[9] The product from this annelation could be converted to an anthraquinone via oxidative decarboxylation. When 1 was reacted with sodium hydride and then with **2a**, the anthrone **4a** was obtained in 60% yield after acidification and filtration through a silica gel

Scheme I. 1,4-Dipole-Quinone Strategy for Anthracyclinone Synthesis



Scheme II. Annelation To Form 8

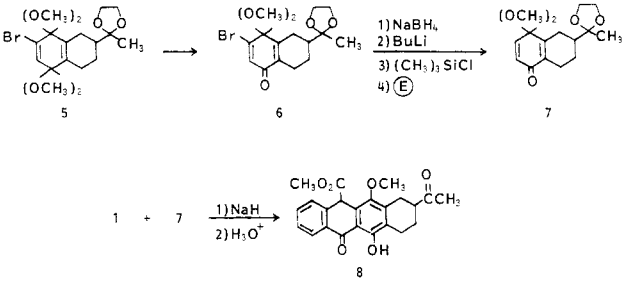
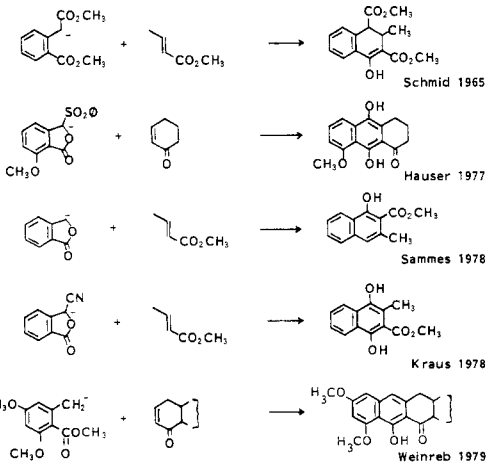


Table I. Potential 1,4-Dipole Equivalents



(1) (a) For recent reviews, see: "Anthracycline Antibiotics", El Khadem, H. S., Ed.; Academic Press: New York, 1982. Arcamone, F. "Doxorubicin"; Academic Press: New York, 1981. (b) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825 and references cited therein.

(2) For preliminary reports of some of this work, see: (a) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263. (b) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 923.

(3) (a) For a review of quinone monoketal chemistry, see: Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74. (b) For the use of quinone monoketals as regiospecific quinone equivalents in annelation reactions since our initial report, see: Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1980**, 932. Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 637.

(4) Eisenmuth, W.; Renfroe, H. B.; Schmid, H. *Helv. Chim. Acta* **1965**, *48*, 375.

(5) (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1979**, *101*, 178, supplementary materials section. (b) Hauser, F. M.; Combs, D. W. *Ibid.* **1980**, *45*, 4071. (c) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378. (d) Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1983**, *48*, 1328. (e) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1983**, *105*, 5688. (f) The experimental conditions employed in references[5d,e] were not examined since the work did not appear until after this study had been completed[5d] or submitted for publication.[5e]

(6) Broom, N. J.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162.

(7) Kraus, G. A.; Sugimoti, H. *Tetrahedron Lett.* **1978**, 2263. Li, T.; Wu, Y. *J. Am. Chem. Soc.* **1981**, *103*, 7007.

(8) Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 3593.

(9) Kozikowski, A. P.; Schmiesing, R. *Synth. Commun.* **1978**, *8*, 363.

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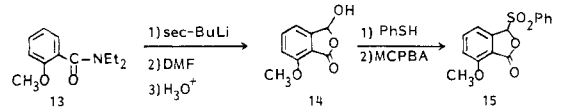
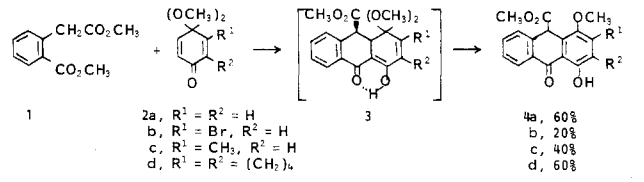
Scheme III. Synthesis of 15



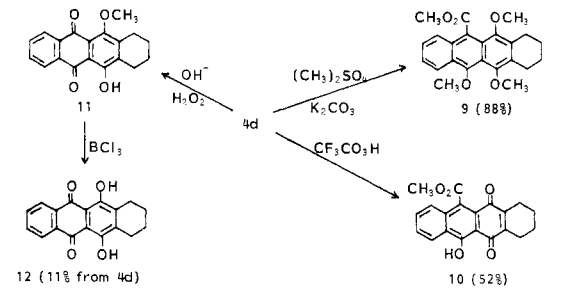
column.[10] The structure was supported by the compound's IR, UV, ^1H and ^{13}C NMR, and high-resolution mass spectra. In the reaction of 1 and **2b–d**, **4b–d** was not



formed directly, but an intermediate was isolated which was quantitatively converted to **4b–d** upon treatment with acid. In the case of **2b** the intermediate was purified and assigned structure **3b** (or its tautomer) on the basis of its ^1H NMR spectrum: δ 15.6 (s, 1 H, enol), 8.0–7.85 (m, 1 H), 7.5–7.25 (m, 2 H), 7.15–7.0 (m, 1 H), 6.85 (s, 1 H), 4.22 (AB q, J = 14 Hz, $\Delta\nu$ = 48 Hz, 2 H), 3.85 (s, 3 H), 3.5 (s, 3 H), 3.40 (s, 3 H). The large coupling constant for the two methine protons in **3b** suggests that this intermediate has the trans stereochemistry. Models show that these two protons have a dihedral angle of nearly 180°.

To extend this chemistry to a system more akin to an anthracyclinone, the readily available bisketal **5**[11] was prepared and monohydrolyzed to the monoketal **6**, the bromine directing the hydrolysis as expected. While several direct routes from **6** to **7** failed, the conversion was effected as indicated in Scheme II. Annelation of **7** afforded **8** in an unoptimized yield of 41%.[12]

Efforts were then directed at conversion of the anthrone moiety of these annelation products to the required anthraquinone system. Because of the sensitivity of the fully functionalized A ring of the final anthracyclinone, only conditions thought to be compatible with this functionality in some protected form were examined. These studies conducted with **4d** were of very limited success. The ester



of **4d** was stable to both mild basic and acidic hydrolysis conditions. Even the completely methylated system **9** resisted ester hydrolysis under mild conditions. Treatment of **4d** with trifluoroperacetic acid gave **10** wherein oxidation occurred at the B rather than the C ring. The desired anthraquinone **12** could be obtained by reaction of **4d** with basic 90% hydrogen peroxide followed by demethylation, but the overall yield was only 10%. These difficulties prompted examination of systems that would afford anthraquinones directly from the annelation step.

(10) The conditions were similar to those of Parker and Kang (Parker, K. A.; Kang, S. *J. Org. Chem.* **1980**, *45*, 1218).

(11) Henton, D. R.; Anderson, D. K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422. We thank Dr. Keith Anderson for the sample of **7** used for this reaction.

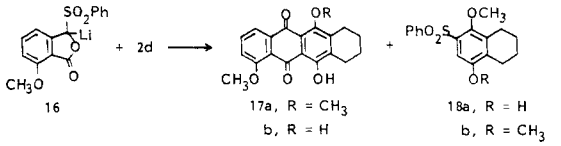
(12) The anodic oxidation was that described by Stewart and Miller (Stewart, R. F.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4999).

Table II. Yields of 17a under Different Annelation Conditions

entry	solvent/base (equiv)	2d, equiv	yield, %
1	THF/LDA (1.1)	1.0	45[a]
2	THF/LDA (1.0)	1.0	42[b]
3	THF/LDA (2.0)	1.0	39[b]
4	THF/LDA (2.0)	2.0	72[b]
5	THF/Me_2SO/ $LiCH_2SOCH_3$ (1.1)	1.0	70[a]
6	THF/Me_2SO/ $LiCH_2SOCH_3$ (2.0)	2.0	81[b]

[a] Recrystallized yield. [b] Yield by UV analysis at λ_{max} = 435 nm using ϵ 8230.

The annelation of the lithiated sulfone lactone[5] was examined next. The required sulfone, **15**, was prepared[5] via the route outlined in Scheme III. The preparation of **14** from **13** was more convenient than the published route since *o*-methoxybenzoic acid is commercially available whereas 2-methoxy-6-methylbenzoic acid must be prepared. The annelation chemistry of **15** was initially explored with **2d**. The literature conditions for performing the annelation employed 2 equiv of lithium diisopropylamide (LDA) as base and 2 equiv of Michael acceptor (i.e., cyclohexenone).[5a,c,f] Since the monoketal envisioned for the synthesis of the anthracyclinones would be available via a multistep sequence, reaction conditions using 1 equiv of **2d** were examined.[3b] Reaction of **16** (1 equiv) and **2d**



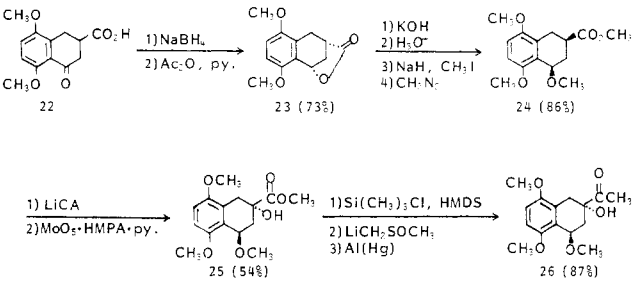
(1 equiv) using LDA (1 equiv) as base under literature conditions[5a,c] gave **17a** (45%) and **18a** (37%). The structure of **17a** was established by regiospecific demethylation of the C_{11}-methoxyl group to give the known **17b**, while **18a** was methylated and shown to be identical with a sample of **18b** prepared independently (see Experimental Section).

The experiments summarized in Table II illustrate the influence of stoichiometry and solvent system on the yield of **17a**. As reported,[5a] the annelation reaction proceeded in high yield when 2 equiv of LDA and 2 equiv of **2d** were employed (entry 4); however, with 1 equiv of **2d**, lower yields of **17a** resulted (entries 1–3). Quinone monoketals are good Michael acceptors[3a] and it was surmised, since **16** was somewhat insoluble in tetrahydrofuran, that the phenyl sulfinate anion released in the final step of the reaction was effectively competing for the quinone monoketal and lowering the yield for the annelation. When the reaction of **16** and **2d** was conducted in the homogeneous medium of 1:1 tetrahydrofuran/dimethyl sulfoxide with use of dimsyl anion as base, improved yields of **17a** resulted. Thus, in our experience, the reaction of **16** and **2d** occurs best in the homogeneous medium of tetrahydrofuran/dimethyl sulfoxide, although with the more functionalized quinone monoketals the yields were still 50–60%. However, it was discovered after the majority of this work was completed that even better yields could be obtained in the annelation of a highly functionalized quinone monoketal by using a different CD-ring synthon (vida supra).

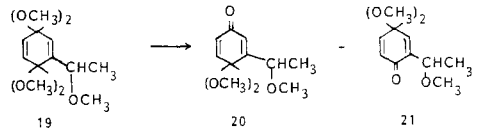
The Quinone Monoketal

A key point in the efficiency of this anthracyclinone synthesis rested with the availability of the quinone mo-

Scheme IV. Synthesis of AB-Ring Precursors



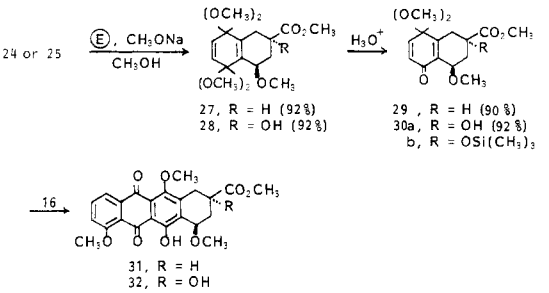
noketal of correct regiochemistry. The monoketal **7**, mentioned earlier, was prepared from the brominated hydroquinone ether in a four-step process in order to ensure this proper regiochemistry. In addition, introduction of the bromine for the sole purpose of directing monohydrolysis required three steps. Thus, through a cumbersome seven-step sequence, **7** was prepared regiospecifically. For our strategy to be preparatively useful, this multistep procedure had to be improved. In earlier studies,[11,13] **19** had been hydrolyzed to a mixture of **20** and



21 in the ratio of ca. 3:1. The surprisingly high proportion of **21** relative to other hydrolyses of monosubstituted benzoquinone monoketals suggested that the allylic methyl ether was effecting the direction of bisketal monohydrolysis. In a system wherein the methoxyl group was more rigidly held and wherein the bisketal was similarly substituted at the olefin positions, the methoxyl group could have a synthetically significant directing effect.

Two points then remained to be established: (1) would the allylic methoxyl group direct the monohydrolysis of **27**, **28**, and **34** and (2) would the 7-methoxyl and 9-hydroxyl groups be compatible with the annelation conditions that formed the tetracyclic ring system? The syntheses of the required precursors are outlined in Scheme IV. Since a discussion of a similar sequence of reactions has been given,[2] only features different from those of the brominated sequence will be noted herein. The conversion of the ester **25** to the ketone **26** proceeded poorly under a variety of conditions. However, if the hydroxyl group was protected as its trimethylsilyl ether, the Corey ketone synthesis[13] afforded **26** in 85% crystalline yield. As noted for the brominated series,[2] the ketone **26** is most expediently prepared from **22** without purification except for silica gel chromatography to separate **26** from its cis (7-OCH_3, 9-OH) isomer. Thus, **26** is available by this sequence in 30% overall yield from **22**.

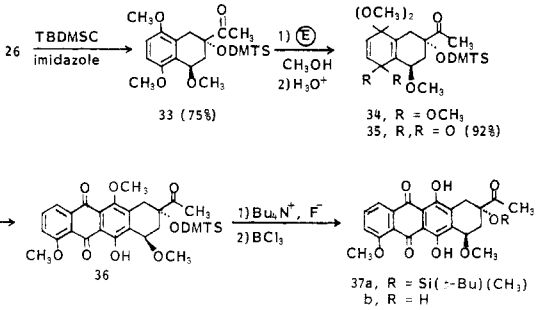
With compounds **24** and **25** readily available, the compatibility of the 7-methoxyl and 9-hydroxyl groups with the annelation reaction conditions could be established. Anodic oxidation and monohydrolysis of **24** and **25** proceeded smoothly to regioselectively yield the monoketals **29** and **30a**.[14] Formation of **31** from **29** and **16** proceeded as expected (49% yield); however, **30a** gave complex reaction mixtures with **16**. Surmising that fragmentation of



the vinylogous β-hydroxyl ketone moiety of **30a** under the basic reaction conditions could be a problem, the hydroxyl group of **30a** was silylated. With the silylated system **30b**, the annelation proceeded, and desilylation occurred in workup to give **32** in 37% yield. These model studies established an efficient regioselective route to quinone monoketals of proper regiochemistry and the compatibility of C_7-methoxyl and C_9-siloxyl groups with the annelation reaction conditions. There then remained the application of this chemistry to the natural compound.

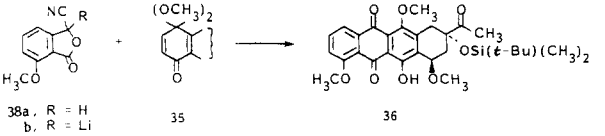
Synthesis of (±)-Daunomycinone

The model studies noted above indicated that the C_9-hydroxyl group in the AB-ring precursor must be protected in the annelation step, and our electrochemical studies indicated that the C_{13} carbonyl had to be protected for the oxidation step. Unfortunately, all attempts to ketalize **26** failed to give even modest yields of the corresponding ketal. After numerous unsuccessful attempts to obtain **26** in a form wherein both the C_9-hydroxyl group and C_{13}-carbonyl group were blocked, the hydroxyl was protected with the *tert*-butyldimethylsilyl group, and it was hoped that this



bulky substituent would protect the methyl ketone during the anodic oxidation step. This was indeed the case, and the required monoketal **35** was easily obtained via anodic oxidation/hydrolysis of **33**. The coupling and deblocking steps occurred smoothly to give **37a** in 40% yield from **35**. The regiochemistry of the monoketal **35** was confirmed by methylation of **36** and desilylation to afford the known 6,7,11-trimethoxy-7-deoxy-7-epimethoxydaunomycinone.[2]

While the annelation reactions described above constitute a regiospecific strategy to anthracyclinones, the yields (40–50%) in reactions employing 1 equiv of monoketal detract from the efficiency of the reaction. After most of this work had been done, the annelation reaction of **2d** with **38b** was examined, and a 92% isolated yield of **17a** was obtained. When this CD-ring synthon was applied to the monoketal **35**, the yield of **36** was 75%. Thus, **38b**



is the most useful reagent for the annelation reactions of

(13) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
(14) The origin of the regioselectivity of the monohydrolyses reported herein will be fully dicussed when mechanistic work in progress is completed. It appears that the ratio of major to minor monoketal in the examples reported herein is about 85:15, somewhat less than that reported in our preliminary communication.[2a]

the two quinone monoketals **2d** and **35**. Since both CD-ring synthons of the sulfone type, **16**, and nitrile type, **38a**, afford the same product, in annelations employing other CD-ring components, the choice of reagent will depend on the availability of the respective sulfone or nitrile as well as the yield in the annelation step.

Summary

A useful strategy has been developed for regiospecific construction of anthracyclinone ring systems. One significant problem remains before a useful synthesis of anthracyclinones will be available: an efficient synthesis of an AB-ring segment having the required *cis*-7,9-diol stereochemistry of proper absolute configuration. This is important since any synthesis affording a mixture of the anthracyclinone and its 7-epi isomer may encounter a difficult separation problem as we have noted for daunomycinone itself.[1] Furthermore, a racemic anthracyclinone, when coupled with an optically active glycon would produce a diastereomeric mixture of anthracyclines, which again may be difficult to separate. Some progress has been made in solving this problem,[1a,15] and this work will be reported elsewhere.

Experimental Section[16]

2d. A solution of 5,8-dimethoxytetralin (5.0 g, 26.0 mmol) in 1% methanolic KOH (80 mL) was electrolyzed at a platinum anode (1.9 V vs. Pt sheet) with a current of 0.7–0.27 A (83% current efficiency), essentially as previously described.[17] After trituration of the crude product with hexane, 6.1 g (92%) of a tan solid, mp 46–51 °C, was obtained and used directly in the next step. A solution of the crude bisketal (5.0 g, **19** 7 mmol), acetone (25 mL), and water (5 mL) was cooled to 0 °C, and acetic acid (1.5 mL) was added. After reacting for 2 h at 0 °C, workup as previously described[17] gave a yellow oil, which was chromatographed on activity III neutral alumina (2.5 × 20 cm column, 25% Et_2O/PE as eluant). After a 50-mL forerun, 3.65 g (89%) of **2d** was obtained as a light yellow oil: IR (neat) μm 2940 (s), 2840 (m), 1670, 1659, and 1619 (s), 1463, 1450, and 1435 (m), 1400 (m), 1370 (m), 1300 (s), 1213 (m), 1135, 1110, 1085, 1072, and 1030 (s), 975, 960, and 950 (s), 850 (s), 820 (m); ^1H NMR ($CDCl_3$) δ 6.6 (AB q, $\Delta\nu$ = 21 Hz, J = 10 Hz, 2 H), 3.2 (s, 6 H), 2.5–2.1 (m, 4 H), 1.9–1.55 (m, 4 H); exact mass calcd for $C_{12}H_{16}O_3$ m/e 208.1091, obsd 208.1100.

Annelations Using Dimethyl Homophthalate. 4a. To a dry, two-necked flask containing a magnetic stirring bar and nitrogen inlet was added sodium hydride (84 mg, 57% oil dispersion). The oil was removed by washing the dispersion with dry hexane (3 × 1 mL). THF (3 mL) was added, followed by **2a**[11] (154 mg, 1.0 mmol) in THF (1 mL), and finally **1** (208 mg, 2.0 mmol) in THF (1 mL). The solution was stirred for 24 h at 25 °C and gradually became an intense red. The mixture was acidified to pH 1 with 1 N HCl, and water (10 mL) was added. The solution was extracted with CH_2Cl_2 (20 mL and then 3 × 3 mL), followed by workup as usual to leave a dark oily foam. This material was chromatographed on silica gel (2 × 12 cm column, 20% Et_2O/PE as eluant) with the elution proceeding as follows: 30 mL, nil; 50 mL, unweighed impurity; 150 mL, 210 mg of **4a**. Recrystallization from Et_2O/hexane gave 180 mg (60%) of **4a** as bright yellow crystals: mp 140–141 °C; IR (KBr) μm 2.8 (m), 5.72 (s), 6.18 (s), 6.32 (s), 6.8 (s with shoulders at 6.9 and 6.98), 7.39 (s), 7.9, 8.02, 8.12, and 8.31 (s, overlapping), 8.58 (m), 9.98 (m), 10.5 (m), 12.95 (m); UV (CH_3OH) 270 nm (ϵ 15400), 286 sh (10400), 390 (3880); ^1H NMR ($CDCl_3$) δ 12.2 (s, 1 H), 8.4–8.2 (m, 1 H), 7.85–7.35 (m, 3 H), 7.05 (AB q, $\Delta\nu$ = 14 Hz, J = 9 Hz, 2 H), 5.23 (s, 1 H), 3.83 (s, 3 H), 3.6 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.2, 171.3, 156.9, 148.8, 137.5, 133.9, 130.8, 128.4, 128.1, 127.5, 126.5, 119.4, 116.7, 116.1, 56.4, 52.8, 44.6; exact mass calcd for $C_{17}H_{14}O_5$ m/e 298.0840, obsd 298.0841.

4b. The reaction was performed as above by using sodium hydride oil dispersion (50 mg), **2b** (233 mg, 1.0 mmol), and **1** (208 mg, 1.0 mmol). After 22 h at 25 °C, the mixture was carefully acidified to pH 4 with 1 N HCl and worked up as usual. The resulting orange-yellow oil was chromatographed on silica gel (2 × 12 cm column, 50% Et_2O/PE as eluant) with the elution proceeding as follows: 20 mL, nil; 10 mL, 73 mg of yellow solid; 20 mL, 79 mg of orange oil. These colored fractions were triturated with hexane to give 69 mg of **3b** as a yellow solid: mp 115–116 °C; IR (KBr) μm 2.9 (s, br), 5.78 (s), 6.2–6.4 (br), 8.55 (m), 9.28 (m); ^1H NMR ($CDCl_3$, 90 MHz) δ 15.6 (s, 1 H), 8.0–7.85 (m, 1 H), 7.6–6.9 (m, 3 H), 6.85 (s, 1 H), 4.22 (AB q, $\Delta\nu$ = 46 Hz, J = 12 Hz, 2 H), 3.85 (s, 3 H), 3.5 (s, 3 H), 3.32 (s, 3 H). The mother liquors were rechromatographed on the same column to give an additional 15 mg of **3b**, for a total yield of 21%.

The product obtained from above was dissolved in benzene (5 mL) and heated to reflux for 45 min with *p*-toluenesulfonic acid (30 mg). The crude product was filtered through a silica gel column (2 × 10 cm, 25% Et_2O/PE as eluant) to give, after recrystallization of the resulting solid from Et_2O/hexane, 31 mg of **4b** in two crops: mp 154.5–155 °C; IR (KBr) μm 2.94 (m, br), 5.75 (s), 6.1 (s), 6.29 (s), 6.81 (s), 8.07 (s), 8.75 (s); UV (CH_3OH) 273 nm (ϵ 16600), 294 (15800), 364 (6502); ^1H NMR ($CDCl_3$) 12.4 (s, 1 H), 8.4–8.2 (m, 1 H), 7.85–7.3 (m, 3 H), 7.2 (s, 1 H), 5.3 (s, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H); exact mass calcd for $C_{17}H_{13}O_5Br$ m/e 375.9941, obsd 375.9950.

4c. The procedure was similar to that of **4a**, affording 40% of **4c** as yellow crystals from Et_2O/hexane: mp 129–130 °C; IR (KBr) μm 2.8 (m), 5.72 (s), 6.10 (s), 6.21 (s), 6.78 (s), 7.33 (s), 7.42 (s), 7.86 (s), 8.03 (s), 8.22 (s), 8.78 (s), 9.99 (s), 10.22 (m), 12.61 (s), 13.51 (s); UV (CH_3OH) 258 nm (ϵ 14200), 284 (13300), 366 (5300); ^1H NMR ($CDCl_3$) δ 12.4 (s, 1 H), 8.4–8.1 (m, 1 H), 7.85–7.2 (m, 3 H), 6.8 (s, 1 H), 5.3 (s, 1 H), 3.75 (s, 3 H), 3.63 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR ($CDCl_3$) 188.6, 171.2, 159.4, 148.2, 141.0, 137.3, 133.7, 130.9, 130.7, 128.4, 128.0, 127.5, 119.0, 114.3, 60.1, 52.9, 45.0, 17.2; exact mass calcd for $C_{18}H_{16}O_5$ m/e 312.0997, obsd 312.1006.

4d. Via a procedure similar to that of **4a**, reaction of **2d** gave 60% of **4d** isolated by a combination of crystallization (49%) from the crude reaction mixture and chromatography (silica gel, $CHCl_3$ as eluant) of the mother liquors: mp 160–161 °C; IR (KBr) μm 2.8 (m), 5.72 (s), 6.11 (s), 6.22 (s), 6.86 (m), 7.09 (m), 7.42 (s), 8.06 (s), 8.76 (s), 9.6 (m), 10.17 (m); UV (CH_3OH) 268 nm (ϵ 11400), 296 (13700), 384 (5100); ^1H NMR ($CDCl_3$) δ 12.8 (s, 1 H), 8.4–8.1 (m, 1 H), 7.8–7.3 (m, 3 H), 5.25 (s, 1 H), 3.70 (s, 3 H), 3.59 (s, 3 H), 2.9–2.5 (m, 4 H), 1.95–1.5 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 188.8, 171.5, 157.8, 147.3, 140.7, 137.4, 133.6, 130.9, 128.3, 128.0, 127.5, 126.8, 126.7, 112.5, 59.9, 52.9, 44.7, 24.9, 22.7, 22.0 (2 carbons); exact mass calcd for $C_{21}H_{20}O_5$ m/e 352.1311, obsd 352.1316.

(15) See also: Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2249.

(16) The following abbreviations have been used throughout the Experimental Section: *n*-butyllithium (*n*-BuLi), chloroform ($CHCl_3$), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethanol (EtOH), ether (Et_2O), hydrochloric acid (HCl), lithium disopropylamide (LDA), methanol (CH_3OH), methylene chloride (CH_2Cl_2), petroleum ether (PE), tetrahydrofuran (THF). All melting points below 220 °C were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Measurements with standard samples indicate that the reported melting points are probably 1–2 °C lower than the correct value. Melting points greater than 220 °C were recorded on a hot-stage apparatus. Infrared spectra were taken primarily on a Perkin-Elmer Model 283B grating spectrometer with some spectra being recorded on a Perkin Elmer Infracord spectrometer. ^1H NMR spectra were recorded at 60 MHz unless otherwise noted. Apparent multiplicities are reported, and in some cases, signals reported as triplets are in fact closely spaced doublet of doublets. ^{13}C NMR spectra (tetramethylsilane reference) were recorded on a Bruker WP-80 instrument at 20 MHz in $CDCl_3$. The 200- and 300-MHz ^1H NMR spectra were recorded by Mr. C. Engelman and Dr. G. Larson. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronics MS-9 double-focusing mass spectrometer. Ultraviolet spectra were recorded on a Carey Model 15 instrument. The maxima are reported in nanometers with the extinction coefficients in parentheses. Tetrahydrofuran was freshly distilled from benzophenone/sodium prior to use. Analytical samples were analyzed by Scandinavian Microanalytical Laboratory. Aluminum oxide and silica gel were from E. Merck Co. "Workup as usual" consisted of extraction of the product (CH_2Cl_2 or Et_2O), drying over calcium sulfate, and concentration in vacuo followed by drying under vacuum.

(17) For complete details on the electrochemical oxidations, see: Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369.

8. Reaction of sodium hydride oil dispersion (5.5 mg, 1.31 mol), 7 (184 mg, 0.62 mmol), and 1 (130 mg, 0.62 mol) was performed essentially as described for **2a** except that the reaction was allowed to proceed for 36 h. The solution was stirred for 36 h at 25 °C and gradually became an intense red. The solution was diluted with THF (10 mL) and water (6 mL), and concentrated HCl (2 mL) was added. This mixture was stirred for 6 h at 25 °C, and during this time a yellow solid precipitated. This material was filtered and rinsed with CH_3OH to give 51 mg of **8** as a mixture (ca. 1:1) of diastereomers. The filtrate was concentrated to 10 mL, and water (20 mL) was added. This mixture was extracted with CH_2Cl_2 (20 mL and then 3 × 3 mL) followed by workup as usual to leave a brown foam. ^1H NMR analysis suggested the hydrolysis was incomplete. The foam was subjected to the hydrolysis conditions above for 6 h more. Workup as above gave a brown foam. Recrystallization from CH_3OH/CH_2Cl_2 gave 45 mg of **8**. The mother liquors were concentrated and subjected to preparative TLC (silica gel, 0.5% CH_3OH/CH_2Cl_2 as eluant) to give 5.5 mg of **8**. In this manner, 101.5 mg (41%) of **8** was obtained: mp 193–197 °C; IR (KBr) μm 5.72 (s), 5.81 (s), 6.10 (s), 6.21 (s), 6.85 (m), 6.98 (m), 7.06 (m), 7.4 (s), 7.9 (s), 8.07 (s), 8.61 (s); ^1H NMR ($CDCl_3$) δ 12.86 (s), 12.8 (s) 8.38–8.1 (m), 7.85–7.25 (m), 5.30 (s), 5.20 (s), 3.80 (s), 3.71 (s), 3.60 (s), 3.2–2.55 (m), 2.45–2.0 (m), 2.24 (s), 1.85–1.55 (m); exact mass calcd for $C_{23}H_{24}O_6$ *m/e* 394.1416, obsd 394.1425.

9. A mixture of **4d** (100 mg, 0.284 mmol), acetone (20 mL), potassium carbonate (160 mg, 1.6 mmol), and dimethyl sulfate (0.082 mL, 0.865 mmol) was gently heated to reflux for 16 h. The cooled solution was filtered, and the acetone was removed at reduced pressure. Workup gave an orange solid, which was recrystallized from Et_2O/hexane to give 92 mg (88%) of **9** as a yellow solid: mp 176–178 °C; IR (KBr) μm 5.72 (s), 7.22 (m), 7.41 (m), 7.95 (s), 8.17 (s), 9.8 (m); ^1H NMR ($CDCl_3$, 90 MHz) δ 8.4–8.2 (m, 1 H), 7.9–7.68 (m, 1 H), 7.55–7.28 (m, 2 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 3.15–2.8 (m, 4 H), 2.1–1.65 (m, 4 H); exact mass calcd for $C_{23}H_{24}O_5$ *m/e* 380.1624, obsd 380.1628.

10. To an open flask were added CH_2Cl_2 (6 mL) and 90% hydrogen peroxide (0.5 mL). The mixture was cooled to 0 °C, and trifluoroacetic acid (0.5 mL) was added with stirring, followed by warming to room temperature. To this mixture was added **4d** (100 mg, 0.284 mmol) as a solid. The solution was stirred for 1 h, and then 5% aqueous KOH was added dropwise via pipet until the reaction reached pH 7. Water (10 mL) was added, and the phases were separated. Workup as usual was followed by chromatography on silica gel (2 × 20 cm column, CH_2Cl_2 as eluant) with the elution proceeding as follows: 70 mL, nil; 115 mL, unweighed impurity; 200 mL, orange solid. This material was recrystallized from CH_2Cl_2/hexane to give 50 mg (52%) of **10** as hard orange crystals: mp 214.5–215 °C; IR (KBr) μm 2.80 (m), 5.76 (s), 6.05, 6.13, and 6.22 (s, overlapping), 7.00 (s), 7.95 (s), 8.10 (s), 9.98 (s), 10.48 (m); ^1H NMR ($CDCl_3$) δ 14.0 (s, 1 H), 8.6–8.3 (m, 1 H), 7.85–7.5 (m, 3 H), 4.10 (s, 3 H), 2.8–2.4 (m, 4 H), 1.95–1.55 (m, 4 H); exact mass calcd for $C_{20}H_{16}O_5$ *m/e* 336.0998, obsd 336.1002.

14.[18] To a dry, three-necked flask with mechanical stirring bar, addition funnel, and nitrogen inlet were added *N,N*-diethyl-2-methoxybenzamide (38.1 g, 184 mmol), tetramethylethylenediamine (30.4 mL, 202 mmol), and THF (200 mL). The solution was cooled to −78 °C, and *sec*-BuLi (202 mL, 1.0 M, 202 mmol) was added dropwise with vigorous stirring over 40 min, followed by 45 min of stirring at −78 °C. To the cloudy yellow solution was added dry DMF (62 mL, 800 mmol) via syringe. The solution was stirred for 25 min at −78 °C, warmed to room temperature, and stirred for 4 h. Water (200 mL) was added, and the solution was acidified to pH 1 with concentrated HCl. The phases were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layer was concentrated at reduced pressure to remove the THF. The residue was dissolved in CH_2Cl_2 (300 mL). The organic phase was washed with 1 N HCl (100 mL) and water (200 mL) and dried over calcium sulfate, and the solvent was removed in vacuo to leave a thick yellow oil. The oil was dissolved in acetic acid (400 mL), and 10% aqueous HCl (400 mL) was added. The mixture was refluxed for 18 h, and then the solvent was removed in vacuo at 40–45 °C. The solid residue was taken up in ethyl acetate (300 mL), and water (300 mL) was added. The mixture was filtered and the solid product was saved. The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic layer was extracted with saturated aqueous $NaHCO_3$ (3 × 200 mL). This basic layer was cooled to 0 °C, carefully acidified to pH 1 with concentrated HCl, and back-extracted with ethyl acetate (3 × 150 mL). This combined organic layer was washed with brine (50 mL) and dried through a cone of calcium sulfate, and the solvent was removed in vacuo to leave a tan solid. This solid was combined with the filtered product and recrystallized from boiling water (400 mL). Cooling gave 20.05 g (60.5%) of the known phthalide **14** as long needles, mp 151.5–153.5 °C (lit.[19] mp 152–154 °C).

Annelation of 15 and 2d. To a solution of LDA formed from diisopropylamine (0.275 mL, 2.0 mmol) and *n*-BuLi (1.8 mmol) in THF (20 mL) at −78 °C was added **15** (0.5 g, 1.64 mmol) as a solid. After stirring at −78 °C for 1 h, a bright yellow slurry resulted to which was added **2d** (340 mg, 1.64 mmol) in THF (5 mL). The solution turned green after 30 min of stirring at −78 °C and purple after warming to room temperature. After the solution was heated to reflux for 1.5 h, the solution was cooled and acidified to pH 1 with 1 N HCl. Workup gave an orange solid, which was chromatographed on silica gel (2.5 × 24 cm column). The elution proceeded as follows: 100 mL of 20% Et_2O/PE, nil; 350 mL of 20% Et_2O/PE, 200 mg of **18a** as an off-white solid; 1000 mL of 25% Et_2O/PE, 250 mg (45%) of **17a** as an orange solid suitable for subsequent transformation. A sample of **17a** recrystallized from CH_3OH/CH_2Cl_2 as fluffy needles gave following: mp 196–197 °C; IR (KBr) cm^{-1} 3440 (m), 1658 (s), 1610 (s), 1584 (s), 1433 (m), 1420 (m), 1400 (m), 1380 (s), 1295 (m), 1235 (s), 1210 (m), 1036 (m), 980 (m); ^1H NMR ($CDCl_3$, 90 MHz) δ 7.85 (meta coupled d, J = 8, 2 Hz, 1 H), 7.60 (t, J = 8 Hz, 1 H), 7.25 (meta coupled d, J = 8 Hz, 2 H), 4.00 (s, 3 H), 3.8 (s, 3 H), 2.9–2.6 (m, 4 H), 1.9–1.65 (m, 4 H); exact mass calcd for $C_{20}H_{18}O_5$ *m/e* 338.1154, obsd 338.1147. Compound **17a** was converted to the known[20] **17b** with BCl_3 in CH_2Cl_2.

The side product **18a** was recrystallized from EtOH/water to give 100 mg (36%) of white solid, mp 170–173 °C.

18b from 18a. A mixture of crude **18a** (40 mg, 0.13 mmol), potassium carbonate (73 mg, 0.53 mmol), dimethyl sulfate (300 mL), and acetone (3 mL) was heated to reflux for 6 h. Workup as for **9** followed by chromatography of the product on silica gel (2 × 18 cm column, 10% Et_2O/PE as eluant) gave 39 mg (89%) of **18b** after recrystallization from Et_2O/PE: mp 147–148 °C; IR ($CHCl_3$ solution) cm^{-1} 1475 (s), 1410 (m), 1327, 1323, and 1315 (s, overlapping), 1155 (s), 1112, 1095, and 1083 (m, overlapping), 1009 (m), 595 (s); ^1H NMR ($CDCl_3$) δ 8.25–7.85 (m, 2 H), 7.65–7.3 (m, 4 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.85–3.5 (m, 4 H), 2.9–2.52 (m, 4 H); exact mass calcd for $C_{18}H_{20}O_4S$ *m/e* 332.1082, obsd 332.1074.

Authentic Synthesis of 18b. A solution of 5,8-dimethoxy-6-bromotetralin (271 mg, 1 mmol), prepared from bromination of 5,8-dimethoxytetralin with dioxane dibromide, in dry Et_2O (8 mL) was cooled to 0 °C, and *n*-BuLi (1 mmol) in hexane was added dropwise. The mixture was warmed to room temperature, stirred for 1.5 h, and cooled to 0 °C, and diphenyl disulfide (218 mg, 1 mmol) was added as a solid. The solution was warmed to room temperature with stirring for 1.5 h. Standard workup followed by filtration of the product through a silica gel column (2 × 18 cm, 5% Et_2O/PE as eluant) gave 276 mg (91%) of crude 5,8-dimethoxy-6-(phenylthio)tetralin as a clear, colorless oil. This compound was reacted directly with *m*-chloroperbenzoic acid (406 mg, 2.0 mmol) in CH_2Cl_2 at 0 °C. After reacting for 16 h at room temperature, standard workup afforded 192 mg (63% overall) of **18b**, identical with that obtained above.

23. A slurry of **22**[21] (29.8 g, 119 mmol) in absolute EtOH (950 mL) was mechanically stirred under a nitrogen atmosphere and cooled to −23 °C. To this was added sodium borohydride (14.5

(18) The metalation procedure is that developed by de Silva et al. [de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099]. Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463.

(19) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061.

(20) Miller, D. G.; Trenbeath, S.; Sih, C. *Tetrahedron Lett.* **1976**, 1637.

(21) Wong, C. M.; Schwenk, R.; Popien, D.; Ho, T. L. *Can. J. Chem.* **1973**, *51*, 466.

g, 381 mmol) all at once. The reaction mixture was maintained at −15 °C for 2 h, at 0 °C for 1 h, and at room temperature for 2 h. The reaction was quenched with water (500 mL), and the EtOH was removed by distillation. The aqueous solution was cooled and then washed with $CHCl_3$ (200 mL) and Et_2O (200 mL). The aqueous solution was cooled to 5 °C and carefully acidified to pH 2 with 10% H_2SO_4, causing precipitation of the cis/trans mixture of hydroxy acids. Suction filtration and drying in vacuo afforded 29.8 g of white solid. This was dissolved in pyridine (135 mL) and acetic anhydride (25 mL) and heated at 100 °C for 2 h. The solvents were removed in vacuo (0.5 mm at 60 °C), and the residue was dissolved in CH_2Cl_2 (250 mL). This was washed with 5% $NaHCO_3$ (3 × 50 mL) and brine (50 mL) and dried through Drierite. Removal of solvent afforded 20.5 g (73%) of **23** as white crystals: mp 124.5–126 °C; IR (KBr) cm^{-1} 1763 (s), 1491 (s), 1449 (m), 1339 (s), 1259 (s), 1212 (m), 1136 (s), 1110 (s), 1097 (s), 1078 (s), 1027 (s), 976 (m), 944 (s), 898 (s), 790 (s), 703 (m); ^1H NMR ($CDCl_3$) δ 6.70 (s, 2 H), 5.88 (d, J = 5.5 Hz, 1 H), 3.76 (s, 6 H), 2.96 (br s, 2 H), 2.90–2.44 (m, 1 H), 2.03 (d, J = 11 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 179.1, 151.7, 149.6, 126.0, 122.9, 111.0, 109.5, 71.7, 56.1, 55.4, 37.2, 33.8, 26.4. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.49; H, 5.99.

24. A slurry of **23** (19.5 g, 83.3 mmol), KOH (7.5 g, 114 mmol), and water (250 mL) was stirred at 65 °C for 3 h, causing all of the solid to dissolve. The reaction mixture was cooled, washed with CH_2Cl_2 (75 mL), and acidified to pH 2 with concentrated HCl. The precipitated solid was collected by filtration, and drying in vacuo afforded 19.5 g (93%) of cis hydroxy acid as a white powder: mp 155–156 °C (gas evolution); IR (KBr) cm^{-1} 3500 (m, br), 2960 (m), 1728 (s), 1712 (m), 1605 (w), 1481 (s), 1459 (m), 1260 (s), 1178 (m), 1097 (m), 1078 (m), 1040 (m), 1021 (m), 951 (w), 938 (w), 907 (w), 870 (w), 793 (m); exact mass calcd for $C_{13}H_{16}O_5$ m/e 252.0998, obsd 252.1004.

To a slurry of 57% sodium hydride oil dispersion (8.1 g, 191 mmol, washed well with hexane) in dry THF (650 mL) being stirred under a nitrogen atmosphere was added the hydroxy acid (19.3 g, 76.6 mmol). This was refluxed for 2 h and cooled at 40 °C, and methyl iodide (7.5 mL, 118 mmol) was added. This was allowed to stir at 40 °C for 6 h and then at room temperature overnight. The reaction mixture was then diluted with water (250 mL), and the THF was removed at reduced pressure. The aqueous solution was washed with Et_2O (2 × 200 mL), cooled to 5 °C, acidified with concentrated HCl, and re-extracted with Et_2O. The combined Et_2O extracts were washed with brine and dried through Drierite. Solvent removal afforded a yellow-orange oil, which was crystallized from Et_2O/hexane to give 19.0 g (93%) of the methoxy acid as an off-white solid: mp 113–114 °C; IR (KBr) cm^{-1} 3320–2480 (m, br), 1710 (s), 1606 (w), 1484 (s), 1451 (m), 1439 (m), 1345 (m), 1260 (s), 1233 (s), 1215 (m), 1184 (m), 1107 (s), 1094 (s), 1080 (s), 1062 (s), 1002 (m), 954 (m), 793 (s); ^1H NMR ($CDCl_3$) δ 6.77 (s, 2 H), 4.68 (br t, J = 3 Hz, 1 H), 3.77 (s, 6 H), 3.34 (s, 3 H), 3.03–2.40 (m, 3 H), 2.20–1.67 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 180.7, 152.0, 151.1, 126.2, 125.6, 110.0, 108.4, 70.1, 56.3, 56.1, 55.9, 35.3, 28.4, 23.5. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.17; H, 6.68.

To a slurry of the methoxy acid (18.5 g, 69.5 mmol) in Et_2O (200 mL) was carefully added an ethereal solution of diazomethane until the reaction mixture assumed the color of the excess diazomethane. The solvent was evaporated on a steam bath, and Et_2O (200 mL) was added to the residue. This was washed with 5% $NaHCO_3$ (50 mL) and brine (50 mL) and dried through Drierite. Removal of solvent afforded a yellow solid, which was recrystallized from Et_2O/hexane to afford 18.1 g (93%) of **24** as a white crystalline solid: mp 87–89 °C; IR (KBr) cm^{-1} 2970 (m), 2940 (m), 2840 (m), 1735 (s), 1600 (w), 1480 (s), 1460 (s), 1435 (s), 1362 (m), 1341 (m), 1255 (s), 1197 (s), 1172 (s), 1110 (m), 1098 (m), 1078 (s), 1062 (s), 950 (m), 789 (s), 702 (m); ^1H NMR ($CDCl_3$) δ 6.53 (s, 2 H), 4.53 (br t, J = 3 Hz, 1 H), 3.72 (s, 6 H), 3.56 (s, 3 H), 3.18 (s, 3 H), 3.02–2.32 (m, 3 H), 2.04–1.58 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 175.4, 152.1, 151.2, 126.5, 125.7, 110.0, 108.3, 70.2, 56.4, 56.0, 55.9, 51.5, 35.2, 28.6, 23.8. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.06.

25. Into each of two flame-dried, 250-mL, three-necked flasks containing THF (145 mL) and isopropylcyclohexylamine (4.1 mL) at −78 °C under a nitrogen atmosphere was added 1.59 M *n*-BuLi (15.7 mL) in hexane. These were stirred at −78 °C for 20 min before dropwise addition of a solution of **24** (5.0 g, 35.7 mmol total) in THF (20 mL) to each flask. The lime-green solutions were stirred at −78 °C for 1 h before addition of MoO_5·HMPA·pyr complex[22] (11.2 g) to each reaction. These were stirred for 1 h at −78 °C, 1 h at 0 °C, and 1 h at room temperature before being quenched with CH_3OH (50 mL). The reaction mixtures were combined, and the solvents were removed in vacuo. Saturated NH_4Cl solution (200 mL) was added to the residue, and the product was extracted into CH_2Cl_2 (3 × 150 mL). This was washed with 5% $NaHCO_3$ (2 × 50 mL), 5% HCl (2 × 50 mL), water (50 mL), and brine (50 mL) and dried through Drierite. Removal of solvent afforded 15.5 g of brown oil, from which 3.2 g (30%) of **25a** could be crystallized with CH_2Cl_2/hexane. The mother liquors were impregnated on 12 g of silica gel and chromatographed on silica gel (200 g, column slurry packed with 15% Et_2O/hexane) as follows: 900 mL of 15% Et_2O, nil; 600 mL of 15% Et_2O/H, 600 mL of 25% Et_2O/hexane, 0.83 g of unidentified yellow oil; 400 mL of 25% Et_2O/hexane, 500 mL of 30% Et_2O/hexane, 250 mL of 40% Et_2O/hexane, nil; 800 mL of 40% Et_2O/hexane, 1.07 g of unidentified yellow oil; 500 mL of 40% Et_2O/H, 0.65 g of **24** as a yellowish oil, which was crystallized from Et_2O/H to afford 0.53 g (5.3%).

Elution was continued as follows: 100 mL of 40% Et_2O/hexane, 600 mL of 50% Et_2O/hexane, 350 mL of 70% Et_2O/hexane, nil; 700 mL of 70% Et_2O/hexane, 200 mL of Et_2O, 4.47 g (42%) of **25** (cis/trans mixture) as an orange oil. From this, 2.75 g (56% overall) of **25a** was crystallized by using CH_2Cl_2/hexane: mp 105–107 °C; IR (KBr) cm^{-1} 3410 (s), 2950 (m), 2920 (w), 2830 (w), 1715 (s), 1608 (w), 1485 (s), 1428 (m), 1443 (m), 1323 (m), 1285 (m), 1261 (s), 1245 (m), 1230 (m), 1203 (m), 1128 (m), 1118 (m), 1083 (s), 1070 (s), 1021 (w), 793 (m), 782 (m); ^1H NMR ($CDCl_3$, 60 MHz) 6.69 (s, 2 H), 4.70 (br t, J = 4 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.67 (s, 3 H), 3.31 (s, 3 H), 2.94–2.44 (m, 3 H), 1.97 (center of d of d, J = 14, 4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 176.1, 152.1, 151.1, 125.5, 124.7, 110.4, 108.5, 72.6, 71.4, 56.5, 56.0, 55.9, 52.6, 38.0, 32.3; exact mass calcd for $C_{15}H_{20}O_6$ m/e 296.1260, obsd 296.1265.

26. To a solution of **25** (8.0 g, 27 mmol), pyridine (48 mL), and hexamethyldisilazane (25 mL) being stirred at room temperature under a nitrogen atmosphere was added trimethylsilyl chloride (15 mL). After 9 h of stirring, the reaction mixture was diluted with CH_2Cl_2 (250 mL) and washed with 5% Na_2CO_3 (100 mL), 5% HCl (3 × 100 mL), and brine (100 mL). The organic phase was dried through Drierite, and the solvent was removed to afford 10.2 g of the silyl ether as a yellow oil.

In the usual manner[2] this material was reacted with dimsyl anion in Me_2SO/THF. Workup afforded a yellow foam, which was dissolved in CH_3OH (150 mL), KF·H_2O (5 g) was added, and the solution was heated to reflux for 30 min. Reduction with Al(Hg) and workup gave, after trituration of the residue with hexane, 6.44 g (85%) of **26** as a white crystalline solid: mp 114–116 °C; IR (KBr) cm^{-1} 3338 (br, m), 1703 (m), 1478 (s), 1253 (s), 1110 (m), 1082 (s), 1021 (s); ^1H NMR ($CDCl_3$, 90 MHz) δ 6.75 (s, 2 H), 4.83 (X of ABX, J_{AX} = 3 Hz, J_{BX} = 4.5 Hz, 1 H), 3.72 (s, 3 H), 3.68 (s, 3 H), 3.30 (s, 3 H), 3.08 (AB, $\Delta\nu$ = 33 Hz, J = 16 Hz, 2 H), 2.31 (AB of ABX, $\Delta\nu$ = 52 Hz, J_{AB} = 14 Hz, J_{AX} = 3 Hz, J_{BX} = 4.5 Hz, 2 H), 2.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 212.0, 152.1, 151.3, 125.3, 110.9, 108.9, 76.9, 70.6, 56.3, 56.1 (2 C), 38.8, 31.4, 24.5; exact mass calcd for $C_{15}H_{20}O_5$ m/e 280.1311, obsd 280.1318.

33. To a solution of *tert*-butyldimethylsilyl chloride (2.5 g) and imidamzole (2.3 g) in DMF (30 mL) was added **26** (937 mg, 3.35 mmol).[23] This was stirred at 100 °C for 3 days, after which time the solvent was removed in vacuo (0.3 mm at 60 °C). The residue was diluted with 5% $NaHCO_3$ (20 mL) and extracted with Et_2O (5 × 20 mL). The ethereal solution was washed with water (2 × 20 mL) and brine (40 mL) and dried through Drierite. Solvent removal afforded an oily brown solid, which was recrystallized from CH_3OH to afford 690 mg (52%) of **33** as a white solid. Filtration of the mother liquors through a short silica gel column with 30% Et_2O/hexane afforded an additional 392 mg (82% overall) of **33**: mp 115–117 °C; IR (KBr) cm^{-1} 2960 (m), 2935 (m),

(22) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(23) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. Ogilive, K. K.; Iwacha, D. J. *Tetrahedron Lett.* **1973**, 317.

2860 (m), 1723 (s), 1604 (w), 1482 (s), 1470 (m), 1439 (m), 1331 (m), 1260 (s), 1120 (s), 1088 (s), 1028 (m), 833 (m), 792 (m), 771 (m); ^{1}H NMR ($CDCl_3$) δ 6.69 (s, 2 H), 4.68 (br t, J = 3 Hz, 1 H), 3.78 (s, 6 H), 3.37 (s, 3 H), 2.86–2.38 (m, 3 H), 2.21 (s, 3 H), 1.97 (center of d of d, J = 14, 4.5 Hz, 1 H), 0.89 (s, 9 H), 0.13 (br s, 6 H); exact mass calcd for $C_{21}H_{34}O_5Si$ m/e 394.2175, obsd 394.2181.

Anodic Oxidations.[17] **27.** A solution of **24** (1.0 g, 3.57 mmol) in 1% methanolic sodium methoxide (60 mL) was placed in the anode compartment of a divided cell, and an equal volume of the same solvent was placed in the cathode compartment. This was cooled to 5 °C and electrolyzed until the UV absorption at 293 nm had decreased to less than 5% of its initial value (1.75 h, 1750 C, 39% current efficiency). The electrolysis solution was poured into brine (150 mL) and extracted with CH_2Cl_2 (4 × 40 mL). Normal workup afforded a colorless oil, which was crystallized from methylene chloride/hexane to afford 1.12 g (92%) of **27** as a white fluffy solid: mp 69–71 °C; IR (KBr) cm^{-1} 2930 (m), 2830 (m), 1734 (s), 1208 (s), 1157 (m), 1088 (s), 1068 (s), 1060 (s), 1040 (m), 962 (m); ^{1}H NMR ($CDCl_3$) δ 6.13 (s, 2 H), 3.93 (br t, J = 3 Hz, 2 H), 3.62 (s, 3 H), 3.28 (s, 6 H), 3.22 (s, 3 H), 3.17 (s, 3 H), 3.13 (s, 3 H), 2.87–2.27 (m, 4 H), 1.73–1.31 (m, 1 H); exact mass calcd for $C_{17}H_{26}O_7$ m/e 342.1678, obsd 342.1685.

28. In a manner similar to that described for **24**, **25** (430 mg, 1.45 mmol) was electrolyzed. The crude product was crystallized from hexane to afford 480 mg (92%) of **27** as a white solid: mp 142–143 °C; IR (KBr) cm^{-1} 3445 (s), 2950 (m), 2920 (m), 2825 (m), 1723 (s), 1445 (m), 1418 (m), 1322 (m), 1301 (m), 1263 (m), 1253 (s), 1202 (s), 1212 (m), 1190 (m), 1102 (s), 1085 (s), 1056 (s), 1045 (s), 1032 (s), 1010 (m), 955 (s); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.14 (s, 2 H), 4.09 (br t, J = 4 Hz, 1 H), 3.68 (s, 3 H), 3.30 (s, 3 H), 3.27 (s, 3 H), 3.24 (s, 3 H), 3.20 (s, 6 H), 2.87 (s, 2 H), 2.55 (center of d of d, J = 14, 4 Hz, 1 H), 2.29 (d, J = 18 Hz, 1 H), 1.74 (center of d of d, J = 14, 4 Hz, 1 H); exact mass calcd for $C_{17}H_{26}O_8$ m/e 358.1627, obsd 358.1633.

35. In a manner similar to that described for **24**, a slurry of **33** (1.35 g, 3.3 mmol) in 1% methanolic KOH (80 mL) was electrolyzed (1077 C, 52% current efficiency). After electrolysis, dry ice chips were added to the anode compartment until the pH decreased to about 8. The solvent was then removed in vacuo, brine (20 mL) was added, and the product was extracted into CH_2Cl_2 (3 × 100 mL). Normal workup afforded 1.57 g of the crude bisketal. This was dissolved in acetone (33 mL), the solution was cooled to 0 °C, and 4% acetic acid (16.5 mL) was added. After 1.5 h, saturated $NaHCO_3$ (70 mL) was added. Standard workup followed by recrystallization from hexane gave 1.18 g (79%) of **35** as a white solid: mp 92–93 °C; IR (KBr) cm^{-1} 2955 (s), 2930 (s), 2895 (s), 2850 (s), 1724 (s), 1677 (s), 1650 (s), 1259 (s), 1140–1030 (s, br), 836 (s); ^{1}H NMR ($CDCl_3$/$CHCl_3$) δ 6.62 (AB, $\Delta\nu$ = 26 Hz, J = 10 Hz, 2 H), 4.32 (br t, J = 3 Hz, 1 H), 3.34 (s, 6 H), 3.25 (s, 3 H), 3.06 (m, 1 H), 2.77–1.96 (m, 2 H), 2.15 (s, 3 H), 1.77 (center of d of d, J = 14, 4 Hz, 1 H), 0.88 (s, 9 H), 0.15 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 206.2, 183.2, 152.7, 143.7, 133.76, 132.2, 94.9, 77.8, 70.6, 57.7, 51.8, 50.7, 37.7, 32.4, 27.6, 25.7, 23.7, 23.5, 18.1, −1.9, −2.9; exact mass calcd for $C_{21}H_{34}O_6Si$ m/e 410.2124, obsd 410.2129.

29. A solution of **27** (500 mg, 1.46 mmol) in acetone (10 mL) was stirred at room temperature, and 8% HOAc (5 mL) was added. After 5 min the reaction was quenched with 5% $NaHCO_3$ (10 mL). The product was extracted into Et_2O (3 × 20 mL), which was washed with brine and dried through Drierite. Removal of solvent afforded 420 mg of a yellowish solid, which was recrystallized from Et_2O/hexane to afford 388 mg (90%) of **29** as a white crystalline solid suitable for use in the next step. An additional recrystallization gave the analytical sample: mp 107–109 °C; IR (KBr) cm^{-1} 2980 (m), 2965 (m), 2933 (m), 2895 (m), 2840 (m), 1742 (s), 1677 (s), 1650 (s), 1623 (m), 1443 (m), 1418 (m), 1407 (m), 1368 (m), 1339 (m), 1295 (s), 1270 (m), 1235 (s), 1215 (s), 1190 (s), 1162 (m), 1133 (m), 1087 (s, br), 1063 (s), 1013 (m), 863 (m), 720 (m); ^{1}H NMR ($CDCl_3$) δ 6.70 (AB, $\Delta\nu$ = 22 Hz, J = 10.5 Hz, 2 H), 4.32 (br t, J = 3 Hz, 1 H), 3.66 (s, 3 H), 3.38 (s, 6 H), 3.26 (s, 3 H), 2.97–2.02 (m, 4 H), 1.90–1.44 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 183.2, 174.8, 152.8, 143.5, 135.3, 132.6, 95.0, 68.3, 57.2, 51.5, 50.8, 34.0, 27.8, 24.2; exact mass calcd for $C_{15}H_{20}O_6$ m/e 296.1260, obsd 296.1265.

30a and 30b. To a solution of **28** (275 mg, 0.75 mmol) in acetone (8.0 mL) being stirred at room temperature was added 8% HOAc (4.0 mL). This was stirred for 5 min and quenched with saturated $NaHCO_3$ (20 mL). The product was extracted into CH_2Cl_2 (3 × 10 mL), washed with brine (10 mL), and dried through Drierite. Removal of solvent afforded a white solid which was triturated with hexane to give 220 mg (92%) of **28** suitable for use in the next step. An additional recrystallization gave the analytical sample: mp 145–147 °C; IR (KBr) cm^{-1} 3425 (s), 2940 (m), 1740 (s), 1673 (s), 1647 (s), 1623 (m), 1404 (m), 1354 (m), 1343 (m), 1290 (m), 1273 (m), 1217 (s), 1196 (m), 1154 (m), 1124 (s), 1095–1050 (vs), 857 (s); ^{1}H NMR ($CDCl_3$) δ 6.66 (AB, $\Delta\nu$ = 20 Hz, J = 10 Hz, 2 H), 4.45 (br t, J = 4 Hz, 1 H), 3.74 (s, 3 H), 3.39 (s, 3 H), 3.33 (s, 3 H), 3.25 (s, 3 H), 2.95 (m, 2 H), 3.63–2.73 (m, 3 H); exact mass calcd for $C_{15}H_{20}O_7$ m/e 312.1209, obsd 312.1215.

To a solution of **30a** (113 mg, 0.36 mmol), pyridine (650 mL), and hexamethyldisilazane (323 mL) was added trimethylsilyl chloride (195 mL). The mixture was stirred under nitrogen for 2.5 h and then diluted with CH_2Cl_2 (25 mL). The solution was washed with 5% Na_2CO_3 (15 mL), 5% HCl (2 × 15 mL), and brine. Drying and concentration in vacuo gave 88 mg of **30b**, which was used directly in the coupling reaction with **16**.

31. The coupling was run similar to that of **2d** by using diisopropylamine (0.084 mL, 0.06 mmol), n-BuLi (0.40 mmol), **16** (100 mg, 0.33 mmol), **29** (98 mg, 0.33 mmol), and THF (10 mL). Workup gave an orange foam, which was chromatographed on silica gel (2.5 × 22 cm column using 0.5–0.75% CH_3OH/CH_2Cl_2 as eluant) to yield 71 mg (51%) of **31** as an orange solid.

A sample recrystallized from CH_3OH/CH_2Cl_2 had the following: mp 195–197 °C; IR (KBr) μm 2.8 (s), 5.77 (s), 6.0 (m), 6.15 (s), 6.3 (m), 6.99 (s), 7.28 (s), 7.69 (s), 8.2 (s), 8.3 (sh), 9.35 (m), 9.78 (s), 10.12 (s); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 13.6 (s, 1 H), 7.9 (meta coupled d, J = 8, 2 Hz, 1 H), 7.7 (t, J = 8 Hz, 1 H), 7.3 (meta coupled d, J = 8, 2 Hz, 1 H), 4.85–4.65 (m, 1 H), 4.05 (s, 3 H), 3.9 (s, 3 H), 3.62 (s, 3 H), 3.48 (s, 3 H), 3.1–2.9 (m, 2 H), 2.8–2.6 (m, 1 H), 2.2–1.7 (m, 2 H); exact mass calcd for $C_{23}H_{22}O_8$ m/e 426.1345, obsd 426.1327.

32. As for **2d** the coupling was performed by using diisopropylamine (0.042 mL, 0.30 mmol), n-BuLi (0.25 mmol), **15** (70 mg, 0.23 mmol), **30b** (88 mg, 0.23 mol), and THF (10 mL). Workup as for **2d** gave an orange solid, which was dissolved in Me_2SO (2 mL) and treated with $KF\cdot 2H_2O$ (22 mg, 0.23 mmol). After 1 h, CH_2Cl_2 (25 mL) was added, and the solution was extracted with water (2 × 25 mL) and worked up as usual to give an orange foam, which was chromatographed on silica gel (2 × 22-cm column). The elution proceeded as follows: 100 mL of CH_2Cl_2, nil; 250 mL of 1% CH_3OH/CH_2Cl_2, nil; 50 mL of 1% CH_3OH/CH_2Cl_2, 46 mg of a mixture of **32** and impurities; 125 mL of 1% CH_3OH/CH_2Cl_2; 25 mg of **32** as an orange solid. The mixed fraction was rechromatographed on the same column with the elution proceeding as follows: 350 mL of 0.5% CH_3OH/CH_2Cl_2, unweighed impurities; 100 mL of 1% CH_3OH/CH_2Cl_2, 12 mg of **32**. In this manner 37 mg (37%) of **32** was obtained. A sample recrystallized from CH_3OH/CH_2Cl_2 showed the following: mp 218–219 °C; IR (KBr) cm^{-1} 3460 (s), 1740 and 1718 (s, overlapping), 1663 (s), 1623 (s), 1582 (s), 1436 (s), 1379 (s), 1288 and 1273 (s, overlapping), 1225 (s), 1210 (sh), 1082 (s), 1010 (s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.83 (s, 1 H), 7.90 (meta coupled d, J = 8, 1 Hz, 1 H),), 7.71 (t, J = 8 Hz, 1 H), 7.30 (meta coupled d, J = 8, 1 Hz, 1 H), 4.88 (dd, J = 4.8, 3.4 Hz, 1 H), 4.04 (s, 3 H), 3.87 (s, 3 H), 3.72 (s, 3 H), 3.55 (dd, J = 17.3, 1.4 Hz, 1 H), 3.42 (s, 3 H), 2.87 (d, J = 17.3 Hz, 1 H), 2.86 (s, 1 H), 2.68 (ddd, J = 13.6, 3.4, 1.4 Hz, 1 H), 2.05 (dd, J = 13.6, 4.8 Hz, 1 H); exact mass calcd for $C_{23}H_{22}H_9$ m/e 422.1264, obsd 422.1276.

36/37a. To a mixture of THF (20 mL) and Me_2SO (20 mL) at 0 °C was added 1.59 M n-BuLi (1.53 mL) in hexane (2.43 mmol) to form the dimsyl anion. To this solution was added dropwise a solution of **16** (0.74 g, 2.43 mmol) and **35** (1.0 g, 2.43 mmol) in Me_2SO (10 mL). The reaction was stirred for 10 min at 0 °C (deep red color) and then at room temperature for 3 h (purple solution). The solution was cooled, acidified to pH 2 with 1 N HCl (4 mL), and concentrated in vacuo. The residue was treated with CH_2Cl_2 (75 mL), filtered, and washed with water. After workup the orange residue was chromatographed on silica gel (0.5% CH_3OH/CH_2Cl_2 as eluant) to afford after recrystallization **36** as orange needles; mp 236–238 °C; IR (KBr) cm^{-1} 3440 (m), 2941 (sh), 2920 (s), 1720 (s), 1665 (s), 1625 (s), 1586 (s), 1469, 1450, 1435, 1406, 1381, 1358, and 1345 (s, overlapping), 1239, 1269, 1248, 1221, and 1211 (s,

overlapping), 1112 (s), 1075 (s), 1018 (s), 830 (s); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 13.84 (s, 1 H), 7.91 (meta coupled d, J = 8.2, 1.3 Hz, 1 H), 7.71 (t, J = 8.2 Hz, 1 H), 7.29 (meta coupled d, J = 8.2, 1.3 Hz, 1 H), 4.77 (dd, J = 4.3, 2.6 Hz, 1 H), 4.04 (s, 3 H), 3.94 (s, 3 H), 3.66 (dd, J = 17.2, 1.7 Hz, 1 H), 3.46 (s, 3 H), 2.74–2.65 (incompletely resolved m, 1 H), 2.58 (d, J = 17.2 Hz, 1 H), 2.22 (s, 3 H), 2.01 (dd, J = 14.2, 4.3 Hz, 1 H), 0.87 (s, 9 H), 0.13 (s, 3 H), 0.08 (s, 3 H). Anal. Calcd for $C_{29}H_{38}O_8Si$: C, 64.42; H, 6.71. Found: C, 64.34; H, 6.88.

However, more conveniently, the crude residue from the annelation step was dissolved in CH_2Cl_2 (190 mL) and cooled to −78 °C under a nitrogen atmosphere. To the solution was added 1 N BCl_3 (29 mL) in CH_2Cl_2 over 15 min, followed by stirring the reaction mixture for 45 min at −78 °C. After the reaction was quenched by dropwise addition of CH_3OH at −78 °C, workup, and recrystallization (CH_3OH/CH_2Cl_2), 0.57 g of pure **37a** was obtained. Chromatography (as for **36**) of the mother liquors gave an additional 0.044 g, for a total yield of 0.614 g (47%) over two steps: mp 230–231 °C; IR (KBr) cm^{-1} 1720 (s), 1618 (s), 1579 (s), 1445 (s), 1440 (s), 1410 (s), 1388 (s), 1348 (s), 1312 (s), 1118 (s), 1080 (s), 835 (s); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 13.88 (s, 1 H), 13.40 (s, 1 H), 8.03 (d, J = 7.7 Hz, 1 H), 7.74 (t, J = 7.7 Hz, 1 H), 7.35 (d, J = 7.7 Hz, 1 H), 4.76 (dist t, $J \sim$ 3.4 Hz, 1 H), 4.06 (s, 3 H), 3.71 (d, J = 17.6 Hz, 1 H), 3.48 (s, 3 H), 2.68 (d with addition coupling, J = 14 Hz, 1 H), 2.57 (d, J = 17.6 Hz, 1 H), 2.24 (s, 3 H), 2.04 (dd, J = 4.0, 14 Hz, 1 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.12 (s, 3 H).

37b. To a dry flask were added **36** (100 mg, 0.185 mmol) and THF (15 mL). The solution was stirred, and tetrabutylammonium fluoride trihydrate (117 mg, 0.370 mmol) was added all at once. The reaction became intense blue and was stirred for 15 min at ambient temperature, followed by neutralization with a few drops of 1 N HCl. The THF was removed at reduced pressure, and the residue was taken up in CH_2Cl_2 (25 mL). Workup as usual gave a dark orange solid, which was recrystallized in the following manner: the solid was dissolved in boiling CH_2Cl_2 (10 mL), and CH_3OH was added dropwise with continued boiling so as to maintain a constant volume of 10 mL until crystallization began. The solution was cooled, and filtration gave fluffy orange needles. The process was repeated on the mother liquors to give 70 mg (89%) of desilylated product in two crops, mp 206–209 °C. This product was dissolved in CH_2Cl_2 (30 mL; the solution had to be warmed to effect dissolution) in a dry flask with magnetic stirring under a nitrogen atmosphere. The solution was cooled to −78 °C, and BCl_3 (1.22 mL, 1.22 mmol) was added dropwise via syringe, followed by stirring for 30 min at −78 °C. CH_3OH (4 mL) was added, and the solution was warmed to room temperature. The solvent was removed a reduced pressure, and the dark residue was triturated with CH_3OH (8 mL and then 2 mL), the solvent being pipetted away after being centrifuged. The material was chromatographed on silica gel (2 × 20 cm column) with the elution proceeding as follows: 150 mL of CH_2Cl_2, nil; 200 mL of 0.5% CH_3OH/CH_2Cl_2, nil; 150 mL of 0.5% CH_3OH/CH_2Cl_2, unweighed red side product; 100 mL of 2.5% CH_3OH/CH_2Cl_2, 54 mg (79%) of **37b** as a red-orange solid. A sample recrystallized from acetic acid had the following: mp 274–275 °C; IR (KBr) cm^{-1} 3510 (m), 1715 (m), 1615 (s), 1578 (s), 1445, 1415, and 1382 (s, overlapping), 1288 (s), 1240 (m), 1215 (s), 1070 (m); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 13.87 (s, 1 H), 13.31 (s, 1 H), 8.05 (meta coupled d, J = 0.9, 7.4 Hz, 1 H), 7.78 (t, J = 7.4 Hz, 1 H), 7.39 (meta coupled d, J = 0.9, 7.4 Hz, 1 H), 5.01 (dd, J = 3.9, 4.5 Hz, 1 H), 4.09 (s, 3 H), 3.62 (s, 1 H), 3.42 (s, 3 H), 3.26 (d, J = 16.8 Hz, 1 H), 2.98 (dd, J = 1.3, 16.8 Hz, 1 H), 2.56 (dd, J = 3.9, 14.5 Hz, 1 H), 2.36 (s, 3 H), 2.07 (ddd, J = 1.3, 4.5, 14.5 Hz, 1 H). Anal. Calcd for $C_{22}H_{20}O_6$: C, 64.08; H, 4.89. Found: C, 64.07; H, 4.89.

7,6,11-Trideoxy-7-epimethoxy-6,11-dimethoxydaunomycinone. A mixture of **36** (20 mg, 0.037 mmol), acetone (7 mL), potassium carbonate (10 mg, 0.074 mmol), and dimethyl sulfate (0.007 mL, 0.074 mmol) was heated to reflux for 24 h (color of the solution changed from yellow to nearly colorless). The mixture was cooled and the acetone removed at reduced pressure. Water (10 mL) was added, and the solution was extracted with CH_2Cl_2 (10 mL and then 3 mL). The combined organic layer was worked up as usual to leave a yellow oily solid. This crude product was dissolved in dry THF (1 mL), and tetrabutylammonium fluoride trihydrate (23 mg, 0.074 mmol) was added all at once. The stoppered solution (intense blue) was stirred for 30 min, and then water (10 mL) and a few drops of 1 N HCl were added. The aqueous layer was extracted with small portions of CH_2Cl_2 until it was colorless. The combined organic phase was worked up as usual to leave a yellow oily solid, which was chromatographed on silica gel (0.5 × 22 cm column). The elution proceeded as follows: 50 mL of CH_2Cl_2, nil; 50 mL of 0.5% CH_3OH/CH_2Cl_2, nil; 30 mL of 1.0% CH_3OH/CH_2Cl_2, nil; 20 mL of 1.0% CH_3OH/CH_2Cl_2, 0.56 mg of a yellow impurity; 10 mL of 1.0% CH_3OH/CH_2Cl_2, nil; 80 mL of 1.0% CH_3OH/CH_2Cl_2, 11.4 mg (68%) of the title compound as a yellow solid. A sample recrystallized from CH_3OH/CH_2Cl_2 had mp 166–167 °C and spectroscopic data identical with those of an authentic sample.[2]

37a from 38a. A solution of Me_2SO (3 mL) and THF (3 mL) was cooled to 0 °C, and CH_3Li (0.7 mmol) was added dropwise. After stirring for 5 min, **38a** (0.134 g, 0.7 mmol) in Me_2SO (3 mL)/THF (3 mL) was added, followed by **35** (0.242 g, 6 mmol) in THF (3 mL). The solution went through similar color changes as described for annelations using **16**. After reaction for 2.5 h at room temperature, 5% HCl (3 mL) was added to the solution cooled in ice. Workup in the usual manner gave after drying in vacuo 0.314 g of orange solid, mp 219–225 °C. Recrystallization of this material from CH_3OH/CH_2Cl_2 gave in two crops 0.232 g (75%) of **36** as yellow fibrous crystals, mp 237–239 °C, identical with that reported above.

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Registry No. 1, 716-43-8; **2a**, 935-50-2; **2b**, 72054-82-1; **2c**, 72054-83-2; **2d**, 76657-06-2; **3b**, 76641-30-0; **4a**, 87923-55-5; **4b**, 87923-56-6; **4c**, 87923-57-7; **4d**, 87923-58-8; **7**, 76657-07-3; **8**, 87923-59-9; **9**, 87923-60-2; **10**, 87937-31-3; **14**, 73274-87-0; **15**, 87923-61-3; **16**, 79117-90-1; **17a**, 87923-62-4; **18a**, 87923-63-5; **18b**, 87923-64-6; **22**, 84390-76-1; **23**, 87923-65-7; **24**, 87923-66-8; *cis*-**25**, 87923-67-9; *trans*-**25**, 87923-68-0; *trans*-**25** silyl ether derivative, 87937-32-4; **26**, 87923-69-1; **27**, 79117-95-6; **28**, 79117-94-5; **29**, 79117-93-4; **30a**, 79124-41-7; **30b**, 87923-70-4; **31**, 79117-89-8; **32**, 79117-88-7; **33**, 87923-71-5; **35**, 79117-92-3; **36**, 79117-87-6; **37a**, 87923-72-6; **37b**, 79171-74-7; **38a**, 87923-73-7; 5,8-dimethoxytetralin, 74526-84-4; *N,N*-diethyl-2-methoxybenzamide, 51674-10-3; 5,8-dimethoxy-6-bromotetralin, 87923-74-8; 5,8-dimethoxy-6-(phenylthio)tetralin, 87923-75-9; *cis*-2-carboxy-4-hydroxy-5,8-dimethoxytetralin, 87923-76-0; *cis*-2-(methoxycarbonyl)-4-hydroxy-5,8-dimethoxytetralin, 87923-77-1; 7,6,11-trideoxy-7-epimethoxy-6,11-dimethoxydaunomycinone, 79254-00-5.