4.0 Hz, 1 H), 2.14 (dd, $J$ = 14.3, 9.3 Hz, 1 H), 1.77 (s, 3 H); IR 3100 (w), 2950 (w), 1710 (s), 1650 (w), 1640 (w), 1545 (m), 895 (m), 882 cm$^{-1}$ (m); UV 268 nm ($\epsilon$ 9.6 × 10$^3$); mass spectrum, $m/z$ = 148.0887 (M$^+$, calcd for $C_{10}H_{12}O$ 148.0889).

**3-(3-Butenyl)cyclopent-2-enone (32).** Following the procedure described above for the preparation of **11**, the alcohol obtained from 3-butenylmagnesium bromide and cyclopent-2-enone (5.0 g, 61 mmol), after treatment with acidic $CrO_3$, gave **32** (1.403 g, 17% overall), bp 110–115 °C (10 mm); further purification was achieved by preparative VPC on column D (175 °C): NMR (60 MHz) $\delta$ 6.13–5.47 (m, 1 H), 5.83 (dd, $J$ = 1, 1 Hz, 1 H), 5.22–4.8 (m, 2 H), 2.72–2.10 (m, 8 H); IR 3070 (w), 2955 (m), 1715 (s), 1672 (w), 1643 (m), 1617 (s), 1435 (m), 981 (m), 910 cm$^{-1}$ (m); mass spectrum, $m/z$ 136.0887 (M$^+$, calcd for $C_9H_{12}O$ 136.0887).

**Photolysis of 32.** A solution of **32** (176 mg) in $C_6H_6$ (67 mL) was irradiated at 25 °C through an uranium glass filter for 10 days. VPC analysis on column G (178 °C) indicated two components and a considerable amount (~40%) of **32** remaining. After preparative VPC, a NMR spectrum of the first component indicated it was a mixture. Further separation was achieved on column H (150 °C); the first eluted component was identified as **14b**: NMR (220 MHz) $\delta$ 2.71 (m, $H_a$, $J_{ad} \sim J_{ae} \sim J_{af} \sim 1.3$, $J_{ac} = J_{ab} = 0$ Hz), 2.61 (dd, $H_d$, $J_{cd}$ = 7.9, $J_{ad}$ = 1.4 Hz), 2.57 (d, $H_b$, $J_{bc}$ = 9.2 Hz), 2.03–1.89 (m, 4 H), 1.78–1.58 (m, 4 H), 1.11 (dd, $H_c$, $J_{bc}$ = 9.2, $J_{cd}$ = 7.7 Hz); IR 2960 (s), 2875 (s), 1736 (s), 1448 (w), 1402 (w), 1319 (w), 1277 (m), 1189 (m), 1127 (m), 1024 cm$^{-1}$ (w); mass spectrum, $m/z$ 136.0864 (M$^+$, calcd for $C_9H_{12}O$ 136.0888).

The second component from column H was identified as **5** by comparison of its NMR and IR spectra with those of an authentic sample.[3,22] The second component from column G was identified as **33**: NMR (60 MHz) $\delta$ 6.02–5.37 (m, 1 H), 5.08–4.85 (m, 2 H), 2.88 (d, $J$ = 5 Hz, 2 H), 2.63–2.10 (m, 4 H), 2.03 (s, 3 H); IR 3070 (w), 2950 (m), 1705 (s), 1648 (s), 1620 (w), 1376 (m), 1172 (m), 905 cm$^{-1}$ (m); mass spectrum, $m/z$ 136.0887 (M$^+$, calcd for $C_9H_{12}O$ 136.0889).

**Acknowledgment.** We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We are indebted to Mr. Eric Orava for technical assistance, Mr. S. T. Bella for microanalysis, Dr. David H. Live for determining the 600-MHz NMR spectra, and Dr. Aksel A. Bothner-By for access to the 600-MHz NMR spectrometer located at Carnegie-Mellon University and supported by National Institutes of Health Grant No. RR-00292.

**Registry No.** **3**, 78258-37-4; **4**, 78307-16-1; **5**, 75888-95-8; **11**, 78258-32-9; **12**, 79191-32-5; **13**, 78258-33-0; **14b**, 79191-33-6; **15**, 62716-60-3; **18**, 78258-34-1; **20**, 78258-35-2; **21**, 78258-36-3; **24**, 78258-38-5; **26**, 78265-02-8; **27**, 78258-39-6; **28**, 78258-40-9; **31**, 79191-34-7; **32**, 79191-35-8; **33**, 3569-36-6; 1-bromo-3-methyl-3-butene, 20038-12-4; cyclopent-2-enone, 930-30-3; 3-butenyl bromide, 5162-44-7.

# 1,4-Dipole-Metalated Quinone Strategy to (±)-4-Demethoxydaunomycinone and (±)-Daunomycinone. Annelation of Benzocyclobutenedione Monoketals with Lithioquinone Bisketals

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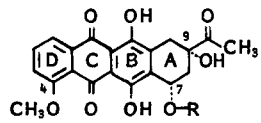
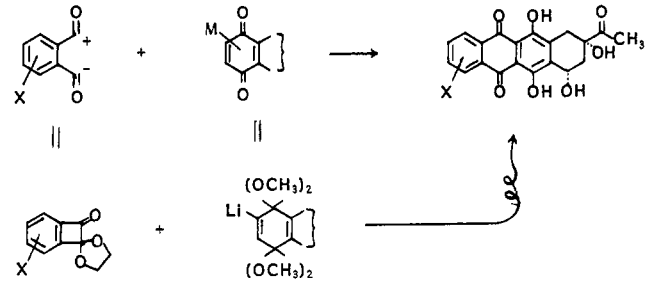
A strategy for total synthesis of anthracyclinones is outlined in which a benzocyclobutenedione monoketal, serving as a 1,4-dipole equivalent, is reacted with a lithiated quinone bisketal, serving as a metalated quinone equivalent, to afford in one step a fully functionalized tetracyclic ring system. A convenient synthesis of the AB-ring system with the eventual $C_7$ and $C_9$ oxygen functions of the anthracyclinone present has been developed. In addition, a trimethylsilyl-mediated benzylic bromination serves as one of the key steps in a novel methylene-to-carbonyl transformation, resulting in a regiospecific route to benzocyclobutenedione monoketals. The potential general synthetic utility arising from trimethylsilyl-stabilized radical intermediates is noted. The chemistry described above resulted in a convergent, regiospecific route to (±)-4-demethoxydaunomycinone and (±)-daunomycinone.

Anthracycline antibiotics have been of much interest in recent years due to their demonstrated therapeutic value in cancer chemotherapy.[1] The intact antibiotic consists of a glycon and an aglycon portion, and since the coupling of these two segments has been achieved,[2] synthetic efforts have concentrated on the synthesis of the rhodomycinone aglycons (i.e., daunomycinone, R = H). Most of the early




studies focused on synthesis of the 7-deoxy- or 9-deoxydaunomycinone without regiochemical control or the 7-deoxy-4-demethoxy analogue.[3] This was followed by benzylic bromination and solvolysis of the labile 7-bromo

Scheme I. Quinone Bisketal 1,4-Dipole Strategy

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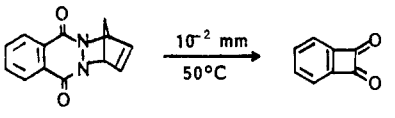
0022-3263/81/1946-4825$01.25/0 

compound.[4] The stereochemistry at $C_7$ can be equilibrated via solvolysis of a $C_7$-oxygen derivative by trifluoroacetic acid as originally studied by Brockmann[5] in related anthracyclinones and is not of initial concern in the synthetic strategy. Since literature experimental indicates that the introduction of the $C_7$ oxygen proceeds in modest yields at best,[4e,f] more recent routes have incorporated the $C_7$ oxygen earlier in the synthetic sequence.[3,6] This appeared to have resulted in much more efficient routes to the rhodomycinone aglycons.

In 1977[7a,b] we reported a regiospecific synthesis of 7,9-deoxydaunomycinone via a sequence amenable to preparation of a $^{14}C$-ring-labeled system for tissue distribution and metabolism studies.[7c] However, the overall yield for introduction of the 9-hydroxy (50%)[8] and 7-hydroxy functions (35%)[4e,f] was only 17%, a dear price to pay on an optically active, $^{14}C$-labeled precursor. Thus, there was desired a convergent, regiospecific synthesis utilizing a fully functionalized, optically active AB-ring system which would proceed under mild conditions to afford the intact A-ring-functionalized anthracyclinone. An approach utilizing a quinone organometallic species reacting with a 1,4-dipole equivalent[9] (Scheme I) would meet this requirement. Our lithiated quinone bisketal[10] would serve as a viable equivalent for the metalated quinone species; however, at the inception of this work, a stable entity which would function as a 1,4-dipole equivalent was not apparent. We report here the use of benzocyclobutenedione monoketals as chemical equivalents to the 1,4-dipole and the utilization of this 1,4-dipole strategy for a synthesis of (±)-4-demethoxydaunomycinone and a formal synthesis of (±)-daunomycinone.

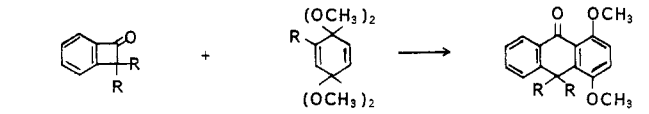
## 1,4-Dipole Equivalent

The chemistry of benzocyclobutenones had been studied previously, and it was known that such species underwent facile ring-opening reactions with base.[11,12] Thus, we envisioned that the addition of an organometallic species to an appropriate benzocyclobutenone would generate the alkoxide which, after undergoing a ring-opening reaction, would add in a Michael fashion to the newly generated $\alpha,\beta$-unsaturated system. Unfortunately, initial attempts to predicate this idea by using a number of benzocyclobutenone derivatives failed. Thus, benzocyclobutenone itself, while undergoing the addition reaction and presumably generating a benzylic carbanion by a ring-opening process, failed to undergo the second Michael addition in reasonable yield.[13] Next, benzocyclobutenone derivatives of the proper oxidation state for generating the anthraquinone C ring were examined. These were readily prepared from the dione **2**,[14] itself conveniently available in modest amounts via pyrolysis of **1**.[15] However, the parent




1 2 (56%)

dione,[10b] the ethanedithiol ketal, the propanedithiol ketal, and the dimethoxy ketal gave mixtures of products on reaction with **4a**, the annelation product being formed in

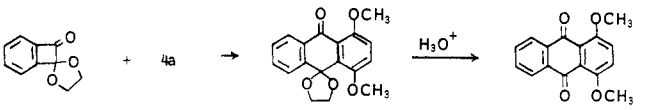


3a, R = H
b, R = $-S(CH_2)_2S-$
c, R = $-S-(CH_2)_3S-$
d, R = $OCH_3$, $OCH_3$

4a, R = Li
b, R = Br

5

modest yield at best. Interestingly, the ethylene glycol ketal **6**[11c] reacted with the lithiated quinone bisketal **4a** to afford **7** in 70% yield. The structure of the product was supported by spectroscopic data, and **7** was then converted to the known **8** by simple acid hydrolysis.




6 7 8

The success of this initial study in forming a simple anthraquinone system prompted examination of the more complex AB-ring precursor **9**. Aside from demonstrating the applicability of this chemistry to form a tetracyclic system, the course of the reaction of butyllithium with **9** was needed. If deprotonation of the hydroxyl group in **9** preceded metal–halogen exchange, then the hydroxyl group in the fully functionalized AB-ring system (vide infra) did not need to be derivatized prior to reaction of **9** with butyllithium. However, if metal–halogen exchange were faster than deprotonation, the hydroxyl group would have to be protected.[16] Reaction of 1 equiv of *n*-butyllithium

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(5) Brockmann, H.; Niemeyer, J. *Chem. Ber.* **1967**, *100*, 3578–3587.

(6) Krohn, K.; Tolkiehn, K. *Tetrahedron Lett.* **1978**, 4023–4026; *Chem. Ber.* **1978**, *112*, 3453–3471. See also: Garland, R. B.; Palmer, J. R.; Schulz, J. A.; Sollman, P. B.; Pappo, R. *Tetrahedron Lett.* **1978**, 3669–3672.

(7) (a) Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *Tetrahedron Lett.* **1977**, 2383–2386. (b) Swenton, J. S.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6188–6195. (c) $^{14}C$ side chain labeled adriamycin has been prepared by three groups: Penco, S.; Vacario, G. P.; Angelucci, A.; Arcamone, F. *J. Antibiot.* **1977**, *30*, 773–775. Vishniwajjala, B. R.; Kataoka, T.; Kazer, F. D.; Witiak, D. T.; Malspeis, L. *J. Labelled Compd. Radiopharm.* **1978**, *14*, 77–82. Chen, C. P.; Tan Tong, M.; Fujiwara, A. N.; Henry, D. W.; Leaffer, M. A.; Lee , W. W.; Smith, T. H. *Ibid.* **1978**, *14*, 111–117.

(8) Suzuki, F.; Trenbeath, S.; Gleim, R. D.; Sih, C. J. *J. Org. Chem.* **1978**, *43*, 4159–4169 and earlier references cited therin.

(9) (a) For a preliminary report of (±)-4-demethoxydaunomycinone, see: Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989–3990. This synthesis of (±)-daunomycinone and the expediency of a trimethylsilyl group in facilitating the radical reactions utilized here were presented at the 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 29–Apr 3, 1981; American Chemical Society: Washington, DC, 1981; ORGN 86.

(10) (a) Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 5008–5010 (b) Swenton, J. S.; Jackson, D. K.; Manning, M. J.; Raynolds, P. W. *Ibid.* **1978**, *100*, 6182–6188.

(11) (a) Cava, M. P.; Muth, K. *J. Am. Chem. Soc.* **1960**, *82*, 652–656. (b) Cava, M. P.; Napier, D. R.; Pohl, R. J. *Ibid.* **1963**, *85*, 2076–2080. (c) Cava, M. P.; Stein, R. P. *J. Org. Chem.* **1966**, *31*, 1866–1869. (d) Stansfield, F.; Amupitan, J. O. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1949–1951.

(12) Thermal ring-opening reactions of benzocyclobutenols with subsequent Diels–Alder cycloaddition are well-known: (a) Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 409–414. (b) *Ibid.* **1974**, 415–420. (c) Sammes, P. G. *Tetrahedron* **1976**, *32*, 405–422. (d) Amaro, A.; Carreno, M. C.; Farina, F. *Tetrahedron Lett.* **1979**, 3983–3986.

(13) Chenard, B. The Ohio State University, 1980, unpublished results.

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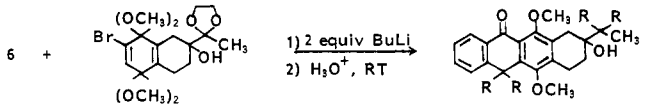
(15) We found the procedure of Rees[14c] to be most convenient for preparation of 2–4-g quantities of the parent dione.

with **9** followed by quenching the reaction with methanol afforded recovered **9**, establishing that deprotonation was considerably faster than metal–halogen exchange in this system. Reaction of **9** with 2 equiv of *n*-butyllithium and then addition of **6** afforded the tetracyclic compound **10a**



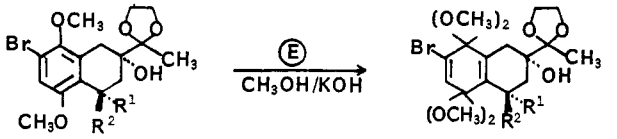

9

10a, R,R = $OCH_2CH_2O$
b, R,R = O

which was then hydrolyzed to **10b** directly in an unoptimized overall yield of 47%. Having now developed the chemistry which would in principle allow the synthesis of a fully functionalized anthracyclinone in one step from a benzocyclobutenone monoketal and an AB-ring precursor, the synthesis of the fully functionalized AB-ring system was required to apply the strategy to the anthracyclinone itself.

## Synthesis of the AB-Ring System

Since the penultimate step in the preparation of the required AB-ring system for coupling with the benzocyclobutenedione monoketal would be electrochemical bisketal formation, substituents in the A ring must be stable to these electrolysis conditions. Thus, the oxygen at the eventual $C_7$ position could not be present as a hydroxyl group since secondary benzylic hydroxyl functions complicate the electrochemical step.[17] On the other hand, aromatic compounds having benzylic methyl ethers undergo smooth oxidation to quinone bisketals.[17] Published model studies indicated tertiary hydroxyl groups (i.e., $C_9$), and ketals were stable toward electrochemical oxidation;[17] thus, **11** became the synthetic objective. On the basis of our previous work, **11** should afford **12** in high yield.

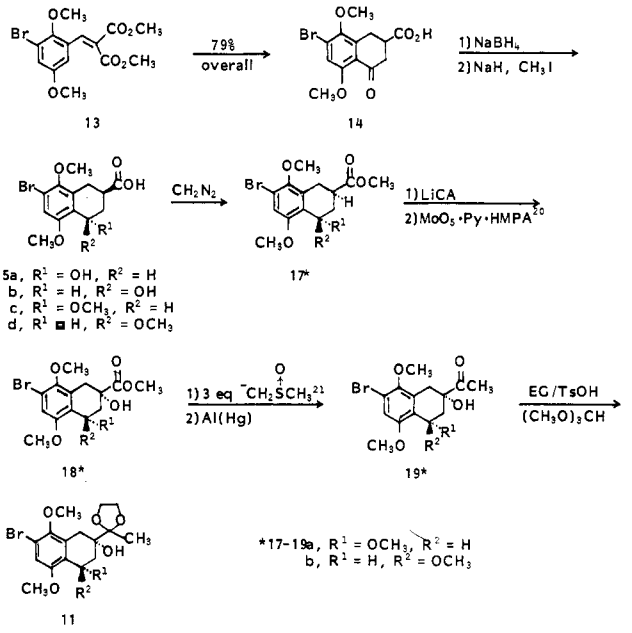



11a, $R^1 = OCH_3$, $R^2$ = H
b, $R^1$ = H, $R^2 = OCH_3$

12

The eventual route to the tetralin **11** (Scheme II) began with **14** which was available in 79% overall yield from **13**.[7b] Since the experimental details are given, only important points of the synthesis will be noted. Sodium borohydride reduction of **14** gave a mixture of **15a** and **15b**, the ratio of which depends upon the temperature of the reaction. At −15 to −20 °C, primarily the *cis*-hydroxy acid is formed (**15a**/**15b** ratio of ~20:80), and preparative reactions were performed at this temperature.[18,19] Initially, the synthetic sequence was carried through with the pure **15b** obtained from lactonization of the crude reduction mixture, extraction of the trans acid, **15a**, and then hydrolysis of the crude lactone **16** back to **15b**. Thus, in our initial studies the sequence **15b** → **15d** → **17b** → **18b** was performed with pure compounds. Since the oxygenation step (**17** → **18**) was not stereospecific and required silica gel chromatography to separate **18a** and **18b**, in scale-up work **14** was carried to **19** without separation of isomers, and then **19a** and **19b** were separated by silica gel chromatography (24–32% overall yield from **14**).

Scheme II. Synthesis of Anthracyclinone A,B Ring System




13 14

15a, $R^1$ = OH, $R^2$ = H
b, $R^1$ = H, $R^2$ = OH
c, $R^1 = OCH_3$, $R^2$ = H
d, $R^1$ = H, $R^2 = OCH_3$

17*

18* 19*

*17-19a, $R^1 = OCH_3$, $R^2$ = H
b, $R^1$ = H, $R^2 = OCH_3$

11

The synthetic sequence **13** → **19** proceeds in a standard fashion except that the oxygenation of the ester enolate of **17** to give **18** was always complicated by incomplete conversion of the reactant. In some runs, VPC analysis indicated >95% conversion to the hydroxyl ester **18** while under seemingly identical conditions ca. 75:25 mixtures of **18** and **17** were observed. The most delicate step of the entire reaction is the ketalization of **19** to give **11**. There appears to be a fine balance between high-yield ketalization of **19** without side reactions and a complex reaction mixture. More than a score of ketalization procedures were attempted before reaction conditions supplied by Professor Paul Dowd led to successful execution of the reaction. Not only is the reaction time important for this particular system, but the time is dependent upon the batch of reagent (i.e., ethylene glycol, trimethyl orthoformate, toluenesulfonic acid). Thus, conditions must be established on a small scale before large-scale reactions are performed.

The stereochemical assignments for the AB-ring systems **11**, **18**, and **19** were based on those expected from their preparations and NMR spectroscopy. The chemical shifts and coupling constants for the protons of the above AB-ring systems and related tetracyclic compounds are summarized in Table I. The NMR spectra of compounds having the cis relationship between oxygen substituents at $C_7$ and $C_9$ are nicely accommodated by assuming the half-chair conformation **20**.[22] The dihedral angles between

(16) For examples of *tert*-butyllithium acting as a stronger kinetic base toward bromine than a carboxylic acid proton, see: Stein, C. A.; Morton, T. H. *Tetrahedron Lett.* **1973**, 4933–4936. Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1977**, *99*, 4822–4824.

(17) Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 370–378, and references cited therein.

(18) The reduction of cyclic ketones by metal-hydride-reducing agents suggests that polar substituents on the ring tend to produce a higher proportion of cis alcohols.[19] However, the temperature dependence of the stereochemistry of the reaction does not appear to have been noted.

(19) (a) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972; pp 60–61. (b) Katsui, N.; Matsunaga, A.; Imaizumi, K.; Masamune, T. *Tetrahedron Lett.* **1971**, 83–86; *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2871–2877. (c) Violland, R.; Violland-Duperret, N.; Pacheco, H.; Ghazarian, M. *Bull. Soc. Chim. Fr.* **1971**, 307–311.

(20) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196.

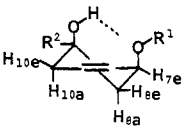
(21) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353.

(22) Note that the conformation of daunomycinone is different as judged by NMR spectroscopy in chloroform vs. pyridine or water. Nuss, M. E.; Thomas, J. L.; Martin, A. P.; Kollman, P. A. *Biochim. Biophys. Acta* **1980**, *609*, 136–147.

Table I. $^1$H NMR Spectral Data at 300 MHz for AB-Ring Protons[a]

| | 7,9-Cis Series | | | | 7,9-Trans Series | | | |
|---|---|---|---|---|---|---|---|---|
| | R = $CCH_3$, 19a | R = $CH_2$, 20a | 4-demethoxydauno-mycinone, 34a | 33a | R = $CO_2CH_3$, 18b | R = $CCH_3$, 19b | R = $CH_2$, 20b | 22b |
| $H_7$ | 4.78 (dd) J = 2.2, 3.4 | 4.71 (dd) J = 2.6, 3.5 | 5.27 (dd) J = 1.6, 4.8 | 4.94 (dist t) J = 3.6 | 4.69 (dd) J = 3.3, 4.5 | 4.88 (dd) J = 5.0, 2.6 | 4.83 (dd) J = 4.4, 6.6 | 4.96 (t) J = 4.2, 5.1 |
| $H_{8e}$ | 2.33 (incompletely resolved t of d) J = 14.5, ~ 2.0, ~ 2.0 | 2.44 (incompletely resolved t of d) J = 14.6 | 2.35 (ddd) J = 14.0, 1.8, 1.6 | 2.43 (part obs t of d) J = 15.2 | 2.6 (d with add'n coupling) J = 13.8 | 1.88 (ddd) J = 15.0, 5.0, 1.0 | 2.12 (ddd) J = 14.9, 6.6, 2.0 | 2.09 (incompletely resolved ddd) J = 14.4, 5.1, ~ 1.0 |
| | | | | | 1.97 (dd) J = 4.5, 13.8 | 2.53 (dd) J = 15.0, 2.6 | 2.23 (dd) J = 14.9, 4.4 | 2.52 (dd) J = 4.1, 14.4 |
| $H_{8a}$ | 1.85 (dd) J = 14.5, 3.4 | 1.68 (dd) J = 14.6, 3.5 | 2.18 (dd) J = 14.0, 4.8 | 1.96 (dd) J = 15.2, 3.6 | | | | |
| $H_{10e}$ | 3.12 (dd) J = 17.9, 2.0 | 3.11 (dd) J = 17.6, 1.6 | 3.16 (dd) J = 18.7, 1.8 | 3.28 (dd) J = 18.9, 1.9 | 3.43 (d) J = 16.2 | 3.24 (d) J = 15.1 | 3.06 (dd) J = 15.1, 2.0 | 2.98 (dd) J = 17.0, ~ 1.0 |
| | | | | | 2.83 (d) J = 16.2 | 2.85 (dd) J = 15.1, 1.0 | 2.85 (d) J = 15.1 | 3.28 (d) J = 17.0 |
| $H_{10a}$ | 2.97 (d) J = 17.9 | 2.85 (d) J = 17.6 | 2.94 (d) J = 18.7 | 2.99 (d) J = 18.9 | | | | |
| ArH | 6.97 | 6.92 | 8.35 (m), 7.85 (m) | 8.36 (m), 7.82 (m) | 6.94 | 6.95 | 6.94 | 8.32 (m), 7.81 (m) |
| $ArOCH_3$ | 3.75, 3.85 | 3.75, 3.82 | — | — | 3.74, 3.81 | 3.77, 3.82 | 3.74, 3.81 | — |
| $-CH_2CH_2-$ | — | 4.06 (m) | — | — | — | — | 4.06 | — |
| $CO_2CH_3$ | — | — | — | — | 3.78 | — | — | — |
| $CH_3$ | 2.39 | 1.44 | 2.43 | 2.46 | — | 2.36 | 1.83 | 2.34 |
| $OCH_3(C_7)$ | 3.50 | 3.47 | 3.64 | — | 3.32 | 3.23 | 3.26 | 3.83 |
| OH | — | — | 13.59, 13.31 | 13.61, 13.34 | — | — | — | 13.52, 13.34 |

[a] Chemical shifts are in δ; coupling constants are in hertz.



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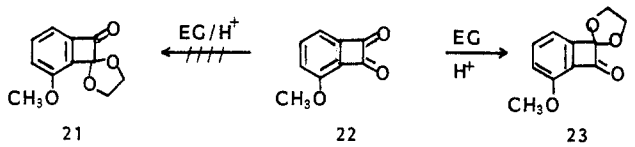
$H_{7e}$–$H_{8e}$ and $H_{7e}$–$H_{8a}$ are similar, and in the first approximation, $J_{7e,8e}$ and $J_{7e,8a}$ would have comparable magnitudes. Thus, the $C_7$ proton appears as a partially resolved doublet of doublets or a distorted triplet. In addition, a long-range W-type coupling of ~1.5 Hz is exhibited between $H_{8e}$ and $H_{10e}$, allowing assignment of the signals due to the axial and equatorial protons at $C_8$ and $C_{10}$. The intramolecular hydrogen bond between the $C_9$-hydroxyl group and the $C_7$-methoxyl group is strongly suggested by the downfield shift of the methoxy in the cis series of compounds (δ ~3.5) relative to the methoxyl group in the trans series of compounds (δ ~3.2).[23] While we have not rigorously assigned either the favored conformation for the trans series of compounds or the specific chemical shifts for the $C_8$ and $C_{10}$ protons, the NMR data are in agreement with trans stereochemistry between the oxygen functions at $C_7$ and $C_9$. Noteworthy points are the appearance of $C_7$ as a clean doublet of doublets, indicative of a much different dihedral relationship between $H_7$,$H_{8a}$ and $H_7$,$H_{8e}$, and the normal position for the saturated methoxyl group at $C_7$.

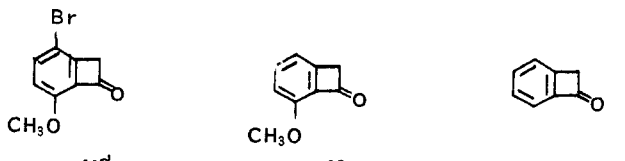
## Regiospecific Route to Benzocyclobutenedione Monoketals

The generality of the chemistry outlined in Scheme I depends on the availability of benzocyclobutenedione monoketals as the CD-ring precursors. While the parent system was easily prepared[11c] via monoketalization of the Cava dione, **2**, routes to unsymmetrical benzocyclobutenedione monoketals had not been studied. Our primary goal was the ketal **21** since this is the CD-ring precursor required for many of the natural series of anthracyclinones. In quest of **21**, numerous classical routes were




21 22 23

explored. Direct ketalization of difficultly available **22**[24] gave a modest yield of monoketal **23** which, with our AB-ring precursor, affords the isodaunomycinone regiochemistry. Various attempts to oxidize or brominate the benzylic positions of the ethylene glycol ketals of **24**, **25**, or even **26** gave either no reaction or a complex mixture of




24[11d] 25[25] 26

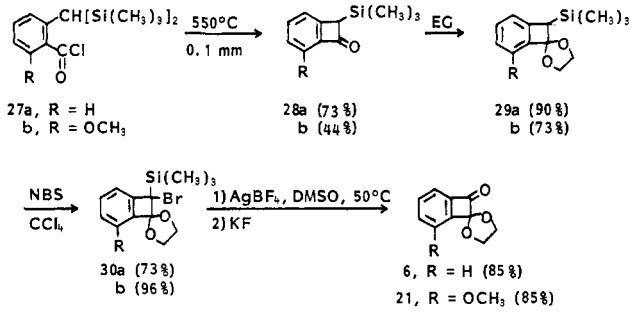
products. In particular, *N*-bromosuccinimide bromination of these ketals gave especially complex reaction mixtures.

(23) See: Wong, C. M.; Popien, D.; Schwenk, R.; TeRaa, J. *Can. J. Chem.* **1971**, *49*, 2712–2718.

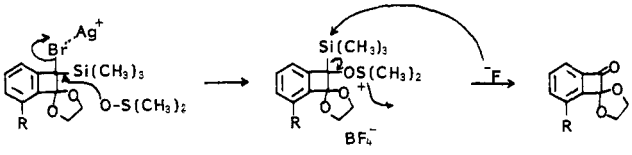
(24) We prepared **22** via the Rees[14] procedure: Blankenship, R. M. Ph.D. Thesis, The Ohio State University, 1975. See also: Jung, M. E.; Lowe, J. A. *J. Org. Chem.* **1977**, *42*, 2371–2373.

(25) Kametani, T.; Takeshita, M.; Nemoto, H.; Fukumoto, K. *Chem. Pharm. Bull.* **1978**, *26*, 556–562.

Scheme III. Synthesis of Benzocyclobutenone Monoketal




Scheme IV. Proposed Mechanism for the Conversion of Bromosilane to Ketone

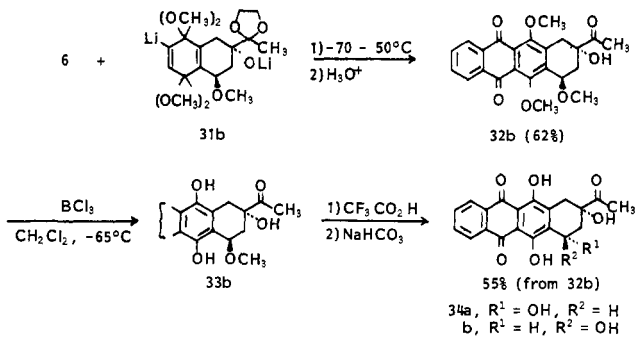



Finally, free-radical bromination of the ketones **24–26**[26] did yield the dibromo ketones in modest yield, but all attempts to ketalize these compounds were unsuccessful.

The failure of classical routes to compounds which might subsequently afford **21** prompted us to examine a new method for oxidation of the benzylic methylene group. Wilt[27] has presented evidence that a trimethylsilyl group stabilizes the transition state in radical-forming reactions relative to a hydrogen atom. However, little quantitative information is known concerning the magnitude of this effect, and no synthetic exploitation of the radical-stabilizing effect of an $\alpha$-trimethylsilyl group has been reported. For exploration of the expedience of a trimethylsilyl group in achieving our objectives, the acid chlorides **27a,b** were pyrolyzed to afford the benzocyclobutenones **28a,b**[28] (Scheme III) which were subsequently ketalized to give **29a** and **29b**. In contrast to our previous experiences in free-radical bromination of benzocyclobutenone ketals lacking a benzylic trimethylsilyl group, **29a** and **29b** rapidly reacted to afford crystalline **30a** and **30b**. The compounds were then transformed into the required dione monoketals by heating with silver tetrafluoroborate[29] in dimethyl sulfoxide followed by treatment of the reaction mixture with potassium fluoride. This latter reaction may be regarded as the silicon analogue of the Kornblum oxidation which would proceed as illustrated in Scheme IV. While the chemistry reported here has been used to prepare only **6** and **21**, it would appear to offer a general route not only to benzocyclobutenedione monoketals but also to the diones[30] themselves via hydrolysis.

These results dramatically demonstrate the synthetic expedience of a trimethylsilyl group in benzylic brominations and the utility of the resulting bromosilane in effecting a methylene-to-carbonyl transformation. While it has not been rigorously demonstrated that the benzylic trimethylsilyl group aids the free-radical bromination because it stabilizes the radical center, the results are consistent with this rationale. Since other reactions proceeding via radical pathways may also benefit by a trimethylsilyl group at the forming radical center, the synthetic utility of this group in expediting such reactions should be considered.

Scheme V. Synthesis of 34a and 34b




## (±)-4-Demethoxydaunomycinone and (±)-Daunomycinone

For completion of the syntheses, there remained the anodic oxidation of **11** to its bisketal and the coupling of the lithiated bisketal to the benzocyclobutenedione monoketal **6**. This chemistry was examined first with the trans (trans here will refer to the $OCH_3$ and OH functions) compound **11b** since this was the major isomer from our synthetic sequence (Scheme II). As expected from model studies, anodic oxidation of **11b** gave **12b** as a crystalline solid in 81% yield. Treatment of **12b** with 2 equiv of *n*-butyllithium gave the dilithio compound **31b**. When **31b** was reacted with **6** and the reaction mixture was hydrolyzed, **32b** was isolated in 62% yield (Scheme V). This compound showed identical physical (TLC, melting point) and spectroscopic (IR, NMR) properties with a sample of **32b** supplied by Professor Wong. While aluminum chloride[4a,b,31] appears as the reagent commonly utilized in the literature for demethylation of aromatic ethers akin to **32b**, boron trichloride was more convenient and furnished **33b** in nearly quantitative yield. The subsequent solvolysis of the $C_7$-methoxyl group initially encountered difficulties since the reaction of **33b** with trifluoroacetic acid at room temperature gave poor yields of a mixture of **34a** and **34b**.[4b] However, if the trifluoroacetic acid was cooled to a slush and then **33b** added, chromatography of the crude product afforded 4-demethoxydaunomycinone (**34a**, 33%), its epi isomer **34b**, 22%), and ca. 7% of aromatized material. The recovered epi material, **34b**, can be epimerized via treatment with trifluoroacetic acid to **34a** (39%), with 27% of **34b** being recovered. Practically, two cycles of this type can be employed, raising the overall yield of the desired 4-demethoxydaunomycinone from **33b** to 44%. We have utilized this chemistry to produce gram quantities of 4-demethoxydaunomycinone.

Since the solvolysis/epimerization sequence for converting **33b** to **34a** was less efficient than desired, we briefly explored the chemistry of **19a**, the minor ketone from our synthesis. If this chemistry proceeds well, then a stereospecific synthesis of **19a** and a demethylation of **31a** would circumvent the solvolysis/epimerization sequence for **31b**

(26) Cava, M. P.; Mangold, D.; Muth, K. *J. Org. Chem.* **1964**, *29*, 2947–2948.

(27) Wilt, J. W.; Aznavoorian, P. M. *J. Org. Chem.* **1978**, *43*, 1285–1286 and references cited therein.

(28) Chenard, B. L; Slapak, C.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1981**, 179–180. A full paper describing extensive pyrolysis studies on these and related systems is in preparation. Full experimental details for the systems noted here are available upon request.

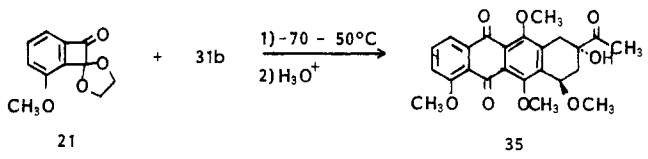
(29) The use of silver tetrafluoroborate to effect Kornblum oxidation on bromides is known: Lemal, D. M.; Fry, A. J. *J. Org. Chem.* **1964**, *29*, 1673–1676.

(30) These compounds have been of special recent interest for the formation of certain metal complexes: Liebeskind, L. S.; Baysdon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7398–7400; *J. Organomet. Chem.* **1980**, *202*, C73–C76.

(31) Kim, K. S.; Vanotti, E.; Suarato, A.; Johnson, F. *J. Am. Chem. Soc.* **1979**, *101*, 2483–2484.

(the a series of compounds has the opposite stereochemistry at $C_7$ of the tetracyclic system). Unfortunately, the ketalization step **19a** → **11a** (56%), the electrolysis step **11a** → **12a** (58%), and the coupling step to form **31a** (44%) all proceeded in substantially lower yield than for the compounds having the hydroxyl and the methoxyl groups trans. Thus, further work along this line was not pursued.[32]

For the synthesis of the (±)-daunomycinone, the organolithium compound **31b** was reacted with **21** and the crude material hydrolyzed to yield 56% of **35**. Since **35**




21 35

has been converted to (±)-daunomycinone,[4a] this comprises a regiospecific synthesis of the compound. In practice this conversion was not efficient;[4a] however, since a superior route to (±)-daunomycinone has been developed,[33] no effort was made to improve the conversion of **35** to (±)-daunomycinone.

## Summary

A convenient synthesis of a fully oxygenated AB-ring precursor of the daunomycinone type has been developed, together with a novel route to benzocyclobutenedione monoketals. This has led to a convergent synthesis of (±)-4-demethoxydaunomycinone and a formal synthesis of (±)-daunomycinone via a one-step annelation between a benzocyclobutenedione monoketal and a highly functionalized lithiated quinone bisketal. A mechanistic discussion of this interesting reaction has been deferred until studies in progress are completed.[9]

## Experimental Section[34]

**2.** Into the 50-mL round-bottomed flask of the pyrolysis apparatus was placed 5.0 g (22.1 mmol) of **1**, and the material was sublimed (bath temperature 150 °C) through the quartz tube held at 550 °C under a vacuum of $2-4 \times 10^{-2}$ mm (Figure 1). After 48 h the yellow crystals formed at the cool end of the pyrolysis tube were washed out with acetone, and the dark solid obtained

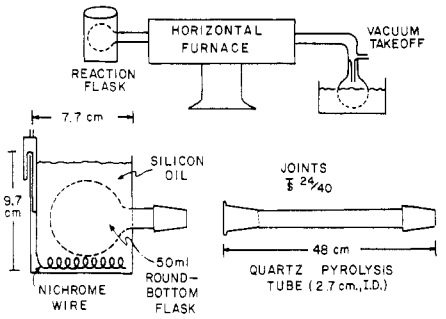



**Figure 1.** Pyrolysis apparatus.

after removal of the acetone was sublimed (65 °C bath, 0.1 mm) to afford 1.4 g of **2**, mp 126–128 °C (lit.[10] mp 130–132 °C). There remained 0.7 g of unreacted **4** in the flask for a corrected yield of 56%.

**7.** A solution of 0.279 g (1.0 mmol) of **4b** in 6 mL of tetrahydrofuran was treated with 0.662 mL (1.0 mmol) of 1.51 M *n*-butyllithium in hexane solution at −65 °C. After 5 min, a solution of 0.185 g (1.05 mmol) of **6** in 1 mL of tetrahydrofuran was added at a rate to maintain the temperature below −60 °C. After being stirred at −65 °C for 0.5 h, the reaction mixture was warmed to room temperature and then heated to reflux for 3 h. The cooled reaction mixture was quenched with methanol and concentrated in vacuo to give after workup a brown solid which was recrystallized from dichloromethane/ether to give 0.216 g (69%) of **7** as fluffy yellow needles, mp 195–197.5 °C dec. The analytical sample had the following: mp 198.5–199.5 °C; IR (KBr) 1660 (s), 1580 (m), 1480 (m), 1320 (m), 1290 (s), 1275 (s), 1260 (s), 1070 (s), 990 (s), 980 (s), 770 (m) $cm^{-1}$; $^1H$ NMR δ 8.23–7.94 (m, 1 H), 7.70–7.30 (m, 3 H), 7.08 (AB, $J$ = 9 Hz, $\Delta\nu$ = 12 Hz, 2 H), 4.50–4.20 (m, 4 H), 3.90 (s, 6 H). Anal. ($C_{18}H_{16}O_5$): C, H.

A mixture of **7** (0.020 g, 0.064 mmol) and 5% hydrochloric acid (2 mL) was stirred at room temperature for 15 h. Workup afforded 0.017 g (100%) of 1,4-dimethoxy-9,10-anthraquinone (**8**) identical in all respects with an authentic sample.

**2-Bromo-1,4-dimethoxy-7-hydroxy-7-(carbomethoxy)tetralin.** To a solution of lithium isopropylcyclohexylamide (2.5 mmol) in tetrahydrofuran (20 mL) at −65 °C under nitrogen was added a solution of 2-bromo-1,4-dimethoxy-7-(carbomethoxy)-tetralin (0.75 g, 2.3 mmol) in tetrahydrofuran (3 mL) over 5 min and the mixture stirred at −65 °C for 1 h. Then 1.382 g (3.18 mmol) of MoOPH[20] was added with vigorous stirring. The red solution was stirred at −65 °C for 1 h, slowly warmed to 0 °C over 0.5 h, and then stirred at 0 °C for 0.5 h. The dark green homogeneous solution was quenched with methanol (recently published procedures recommend saturated sodium sulfite solution), and the solvents were removed in vacuo. The residue was partitioned between ether (50 mL) and water (40 mL), and the aqueous layer was further extracted with ether (25 mL). The ether solution was washed with 5% sodium carbonate solution (2 × 20 mL), water (2 × 20 mL), 5% hydrochloric acid (2 × 15 mL), and saturated sodium chloride solution (20 mL), dried with calcium sulfate, and concentrated. The residue was dissolved in 10 mL of boiling cyclohexane, filtered while hot, concentrated to 6 mL, cooled to room temperature, and filtered to yield 0.43 g of a colorless crystalline solid. The mother liquor was concentrated and chromatographed on 6 g of silica gel (1.8 × 3.5 cm). The elution proceeded as follows: 20 mL of 5% E/H, 0.05 g of impurities; 80 mL of 5% E/H, 0.07 g of starting material; 200 mL of 10% E/H, nil; 50 mL of 15% E/H, nil; 110 mL of 20% E/H, 0.09 g of product; 200 mL of 25% E/H, 0.04 g of impurity. Together, 0.52 g (74% based on reacted ester) of product was obtained: mp 121–123 °C; IR (KBr) 3480 (s), 2955 (m), 2845 (w), 1731 (s), 1577 (m), 1475 (s), 1442 (m), 1410 (w), 1400 (w), 1350 (w), 1335 (w), 1307 (m), 1265 (m), 1250 (s), 1190 (m), 1100 (s), 1075 (m), 1040 (m), 972 (w), 962 (w), 845 (m), 816 (w), 790 (m) $cm^{-}$; $^1H$ NMR ($CDCl_3$) δ 1.98 (t, $J$ = 6.5 Hz, 2 H), 2.17 (t, $J$ = 6.5 Hz, 2 H), 3.05 (s, 3 H), 3.75, 3.78, 3.83 (s, 9 H), 6.87 (s, 1 H); exact mass calcd for $C_{14}H_{17}O_5Br$ $m/e$ 344.025 97, found $m/e$ 344.026 66 (difference $m/e$ 0.0007). Anal. ($C_{14}H_{17}O_5Br$): C, H.

**2-Bromo-1,4-dimethoxy-7-hydroxy-7-acetyltetralin.** A slurry of lithium dimsylate in tetrahydrofuran was prepared by

(32) The lower yields in this system may result from the trans-diaxial relationship of the $C_7$-hydroxyl group and a $C_8$-hydrogen facilitating elimination as side reactions.

(33) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263–5264.

(34) All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Measurements of standard samples indicated that the observed melting points were probably 1–2 °C lower than the corrected value. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrometer. $^1H$ NMR spectra were taken at 60 MHz ($CCl_4$) with a Varian EM-360 instrument. $^{13}C$ NMR spectra ($Me_4Si$ reference) were recorded on a Bruker HX-90 instrument by Dr. Charles Cottrell. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronic MS-9 double-focusing mass spectrometer. Analytical samples were determined by Scandinavian Microanalytical Laboratory. Aluminum oxide and silica gel were from E. Merck Co. Butyllithium in hexane (Ventron) was titrated in tetrahydrofuran with 1,10-phenanthroline as the indicator. Workup as usual refers to extraction with ether, washing of the ether layers with saturated brine solution, drying over calcium sulfate, and concentration in vacuo. In chromatography, E refers to ether, while H refers to petroleum ether, bp 35–50 °C. For small-scale reactions of the lithio bisketals, the following drying procedure is advisable. The reaction flask is dried with a flame for approximately 1 min while being flushed with a stream of dry argon. The system is then placed under a static argon atmosphere, and tetrahydrofuran distilled from benzophenone ketyl is added via syringe. Approximately 1 mg of triphenylmethane is added, and the solution is then cooled to −60 °C. This tetrahydrofuran solution is then titrated with butyllithium via syringe until a faint pink color forms and persists for 10–20 s. Only small amounts of butyllithium should be required to form the color. The reagents are then introduced via syringe in tetrahydrofuran which was similarly dried.

treating a solution of dry dimethyl sulfoxide (19.5 mL) in dry tetrahydrofuran (70 mL) maintained under an argon atmosphere with 22.9 mL (36.6 mmol) of a 1.6 M methyllithium/lithium bromide complex in ether solution at 0 °C. This slurry was treated with a solution of 2-bromo-1,4-dimethoxy-7-hydroxy-7-(carbomethoxy)tetralin (4.01 g, 11.6 mmol) in dry tetrahydrofuran (10 mL). After being stirred for 2 h at 0 °C, the mixture was quenched with methanol and concentrated in vacuo. The residue was treated with 30 mL of saturated ammonium chloride solution and extracted with dichloromethane (4 × 20 mL). Workup afforded 4.74 g (100%) of the crude β-keto sulfoxide as a white foam. This foam was dissolved into a mixture of tetrahydrofuran (230 mL) and water (26 mL) and treated with aluminum amalgam, prepared from 3.29 g (121.9 mmol) of aluminum foil.[21] After 1 h the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was extracted with dichloromethane (4 × 20 mL) and worked up to afford a colorless oil. This oil crystallized from E/H solution to afford 3.69 g (96%) of the title compound as a white solid: mp 87–89 °C; IR (KBr) 3480 (br, s), 2930 (m), 1695 (s), 1470 (s), 1465 (s), 1235 (s), 1095 (s), 1060 (s) $cm^{-1}$; $^1H$ NMR δ 6.83 (s, 1 H), 3.78, 3.70, 3.64 (all s, total 7 H), 3.04–2.53 (m, 4 H), 2.28 (s, 3 H), 2.03–1.63 (m, 2 H); exact mass calcd for $C_{14}H_{17}O_4Br$ *m/e* 328.031 065, found *m/e* 328.031 690, (difference *m/e* 0.000 64).

**2-Bromo-1,4-dimethoxy-7-hydroxy-7-acetyltetralin Ethylene Glycol Ketal.** A mixture of 3.54 g (10.8 mmol) of the ketone, ethylene glycol (2 mL), and 36 mg of *p*-toluenesulfonic acid maintained under a nitrogen atmosphere was heated to reflux in an apparatus equipped for azeotropic removal of water. After 6 h the cooled reaction mixture was diluted with ether (20 mL) and washed with water (1 × 15 mL), saturated sodium bicarbonate solution (1 × 15 mL), water (1 × 15 mL), and saturated brine (1 × 15 mL). Workup afforded a colorless oil which was recrystallized from hexane to afford 3.76 g (94%) of the title compound as a white solid, mp 110–112 °C. The analytical sample had the following: mp 111–113 °C; IR (KBr) 3400 (s), 1475 (m), 1460 (s), 1420 (s), 1400 (m), 1370 (m), 1300 (m), 1225 (vs), 1200 (m), 1175 (m), 1165 (m), 1080 (vs), 1050 (s), 1035 (vs), 1025 (s), 950 (s), 890 (m), 870 (m), 830 (m), 780 (m), 760 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) δ 6.77 (s, 1 H), 3.98 (s, 4 H), 3.73 (s, 6 H), 2.98–2.48 (m, 4 H), 2.30–1.50 (m, 3 H), 1.39 (s, 3 H); exact mass calcd for $C_{16}H_{21}O_5Br$ *m/e* 372.057 277 1, found *m/e* 372.057 875 (difference *m/e* 0.0006).

**9.** Anodic oxidation of the ketal from the previous step was carried out in a standard H-cell apparatus having compartments 3.0 cm in diameter, separated by a medium-porosity frit.[7b,17] The anode and cathode compartments had volumes of 85 mL each. The cathode compartment contained 1.5 g of potassium hydroxide in methanol (60 mL), while in the anode compartment were 1.41 g (3.78 mmol) of the ketal and 1.5 g of potassium hydroxide dissolved in tetrahydrofuran (10 mL) and methanol (50 mL). Oxidation was carried out at a potential range of 1.60–1.85 V vs. a platinum reference electrode at 0–10 °C and with a current of 0.5 A for 3 h. The progress of the reaction was monitored by following the decrease in the UV maximum at 287 nm to about 5% of the original value. Dry ice was added to the contents of the anode compartment until the solution was only slightly basic, and the solvent was removed at or below room temperature under reduced pressure. Water was added to the residue which was extracted with dichloromethane (3 × 10 mL). Workup gave a yellow oil which was crystallized from 5 mL of methylcyclohexane to afford 1.39 g (85%) of **9** as a white, crystalline solid melting at 105–111 °C. The analytical sample had the following: mp 121–121.5 °C (E/H); IR (KBr) 3490 (s), 2940 (m), 1315 (m), 1230 (m), 1190 (vs), 1080 (vs, br), 1055 (vs), 1040 (vs), 965 (s), 745 (m), 715 (m) $cm^{-1}$; $^1H$ NMR δ 6.70 (s, 1 H), 4.00 (s, 4 H), 3.24 (s, 3 H), 3.20 (s, 3 H), 3.10 (s, 6 H), 2.50–2.13 (m, 4 H), 2.03–1.58 (m, 3 H), 1.38 (s, 3 H). Anal. ($C_{18}H_{27}O_7Br$): C, H.

**10a,b.** A solution of 0.50 g (1.15 mmol) of **9** in 7 mL of dry tetrahydrofuran maintained under a dry argon atmosphere was treated with 1.60 mL (2.41 mmol) of a 1.51 M *n*-butyllithium in hexane solution at −80 °C. After 5 min, a solution of 0.223 g (1.26 mmol) of **6** in 1.5 mL of dry tetrahydrofuran was added to the reaction mixture at −80 °C, and the mixture was allowed to warm to −65 °C. After 0.5 h the reaction mixture was heated to reflux for 6 h and then stirred at room temperature for 11 h. The mixture was treated with methanol (1 mL) and concentrated in vacuo. The residue was slurried in water and extracted with chloroform (5 × 8 mL). Workup gave a brown oil which crystallized upon addition of ether to give 0.253 g (47%) of **10a** in two crops as an off-white solid, mp 228–230 °C. Recrystallization (dichloromethane/ether) gave the analytical sample: mp 245–247 °C; IR (KBr) 3440 (w, br), 2930 (br, w), 1670 (s), 1455 (m), 1410 (m), 1330 (s), 1315 (s), 1245 (m), 1085 (m), 1045 (vs), 980 (m), 950 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) δ 8.20–7.98 (m, 1 H), 7.78–7.30 (m, 3 H), 4.43–4.13 (m, 4 H), 4.03 (s, 4 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 3.17–2.80 (m, 4 H), 2.03–1.70 (br s, 2 H), 1.40 (s, 3 H). Anal. ($C_{26}H_{28}O_8$): C, H.

A solution of 0.072 g (0.154 mmol) of **10a** in a mixture of tetrahydrofuran (10 mL), water (4 mL), and concentrated hydrochloric acid (1.3 mL) was stirred at room temperature for 16 h. The mixture was concentrated in vacuo, and the residue was extracted with dichloromethane (3 × 8 mL). Workup gave 0.057 g (98%) of **10b** as a yellow solid. A portion of this material was recrystallized from dichloromethane/ether; mp 183.5–186 °C (lit.[4a] mp 184–186 °C).

**Preparation of 14 from 13.** To a mechanically stirred solution of 50.0 g (139.2 mmol) of **13** in 400 mL of dry tetrahydrofuran maintained under a dry argon atmosphere was added, dropwise, 140 mL (140 mmol) of a 1 M L-Selectride (tri-*sec*-butyl borohydride) in tetrahydrofuran solution at −60 °C. After 30 min, the reaction mixture was allowed to warm to 0 °C, and 23.4 g (153 mmol) of methyl bromoacetate was added. The mixture was then heated to reflux for 5 h. Concentration of the cooled reaction mixture in vacuo afforded a light brown oil which was used without further purification in the next step. This brown oil was dissolved into a mixture of ethanol (180 mL), water (400 mL), and potassium hydroxide (97 g). The reaction mixture was heated on a steam bath for 5 h and then cooled to room temperature overnight. The mixture was extracted with chloroform (160 mL) and ether (100 mL), and the aqueous phase was poured into a mixture of concentrated hydrochloric acid (200 mL) and ice (240 mL). After ~0.5 h the product started crystallizing from the solution, and 100 g of salt was then added. The mixture was cooled at 0 °C overnight and then vacuum filtered. After the filter cake was washed with 150 mL of cold water, it was vacuum dried to afford 63.8 g of an off-white solid. A slurry of this solid in 420 mL of acetic anhydride was heated at reflux for 20 min. The hot solution was then gravity filtered and the filtrate concentrated in vacuo to give 42.1 g of crude anhydride as a tan solid. This tan solid was placed into a polyethylene bottle and dissolved in 400 mL of liquid hydrogen fluoride. The solution was allowed to sit at room temperature for 16.5 h, at which time some of the hydrogen fluoride was still present. The mixture was carefully quenched with ice chips and the volume of liquid increased to 400 mL with the addition of more ice. An oil soon separated which solidified, and the water layer was decanted into another polyethylene bottle. The solid was dissolved into chloroform (800 mL), and this chloroform solution was washed with water (300 mL). The organic phase was dried over anhydrous magnesium sulfate and concentrated to a final volume of 100 mL. At this point the product precipitated, and the mixture was vacuum filtered. The filter cake was washed with a small amount of chloroform and vacuum dried. Concentration of the combined filtrate and washings to 10 mL afforded more product. The total amount of **14** collected was 36.4 g for a 79% yield over four steps.

**16.** To a slurry of 5.6 g (15.2 mmol) of **14** in 135 mL of dry ethanol at −25 °C under nitrogen was added 2.0 g (53 mmol) of sodium borohydride. The solution was allowed to warm to −15 °C (slightly wet ethylene glycol/dry ice bath) and stirred at that temperature for 2 h. The reaction mixture was maintained in an ice bath for 1 h and then allowed to warm to room temperature. The ethanol was removed in vacuo with heating, the colorless residue was dissolved in water (75 mL), and the solution was extracted with chloroform (30 mL) and ether (30 mL). The aqueous layer was cooled in ice and acidified to pH 2 with 25% sulfuric acid. A white solid slowly separated over 1 h, and this was filtered, washed with ice-cold water, and dried to yield 4.82 g (95%) of a colorless solid which was a mixture of **15a** and **15b**.

This mixture was heated in a stream of nitrogen in a dry flask for 30 min and cooled, and the lactone was leached into 125 mL of ether used in small portions. After the white solid (0.35 g of pure lactone) was filtered, the ether solution was washed with

freshly prepared 5% sodium bicarbonate solution (3 × 25 mL) and saturated sodium chloride solution (30 mL). Workup gave 3.27 g of the lactone **16** as a crystalline solid. Together with the filtered solid, the crude yield was 3.62 g (80%) of **16**, mp 102–106 °C. It was recrystallized from hexane/tetrahydrofuran to give 3.14 g (70%) of a crystalline solid, mp 115–118 °C. The analytical sample of **16** was prepared by recrystallization from hexane/tetrahydrofuran (mp 118–119.5 °C) and sublimation at 100 °C ($1.6 \times 10^{-4}$ torr): IR (KBr) 2940 (m), 1765 (s), 1580 (m), 1480 (s), 1455 (m), 1440 (m), 1412 (m), 1345 (m), 1240 (m), 1225 (m), 1148 (m), 1118 (s), 1102 (s), 1036 (m), 1020 (s), 990 (m), 960 (s), 912 (s), 842 (m), 775 (m), $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.02 (d, $J$ = 11 Hz, 2 H), 2.17–2.93 (m, 1 H), 3.13 (br s, 3 H), 3.77 and 3.8 (s, 6 H), 5.85 (d, $J$ = 5.0 Hz, 1 H), 6.90 (s, 1 H); exact mass calcd for $C_{13}H_{13}O_4Br$ $m/e$ 311.999 76, found $m/e$ 312.000 28 (difference $m/e$ 0.0005). Anal. ($C_{13}H_{13}O_4Br$): C H.

**15b.** To a mixture of **16** (1.96 g, 6.26 mmol) and water (15 mL) was added potassium hydroxide (0.425 g, 6.45 mmol) and heated in a bath at 60 °C for 2 h. It was cooled to room temperature and stirred for 0.5 h with 20 mg of potassium hydroxide. The solution was extracted with 20 mL of ether, cooled in ice, and acidified to pH 2 with 25% sulfuric acid. A white solid separated, and after 2 h of cooling, it was filtered, washed, and dried overnight under vacuum to yield 2.07 g (100%) of white powdery solid, mp 139–141 °C. Recrystallization from 3:1 water/methanol gave 1.68 g (81%) of **15b** as fluffy crystals which lactonized to a small extent when dried: mp 137–140 °C; IR (KBr) 3505 (m), 3440 (m, 3360 (m), 2935 (br, m), 1700 (br, s), 1650 (m), 1574 (m), 1470 (s), 1440 (s), 1380 (s), 1290 (s), 1270 (s), 1232 (vs), 1210 (s), 1190 (s), 1100 (s), 1052 (s), 1018 (s), 970 (m), 835 (m), 780 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.8–3.3 (m with s at 3.15, 5 H), 3.78 and 3.87 (s, 6 H), 4.75–5.25 (br, m, 4 H), 6.97 (s, 1 H); exact mass calcd for $C_{13}H_{15}O_5Br$–$H_2O$ $m/e$ 311.999 76, found $m/e$ 312.000 28, (difference $m/e$ 0.0005).

**15d.** To a mixture of dry tetrahydrofuran (120 mL) and hexane-washed sodium hydride (1.58 g, 36.9 mmol) under nitrogen was added **15b** (4.89 g, 14.8 mmol) and the solution heated to reflux for 2 h. The mixture was cooled, methyl iodide (3.15 g, 22.2 mmol) was added, and the slurry was heated in a bath at 40–45 °C overnight. The solvent was removed in vacuo, and the residue was dissolved in water (75 mL) and extracted with ether (2 × 35 mL). The aqueous layer was cooled in ice and carefully acidified to pH 2 by using 5% sulfuric acid to yield a thick yellow liquid which solidified on addition of 6 g of salt and cooling for 1 h in ice. The solid was filtered, washed, and dried in vacuo to yield 4.66 g (91.4%) of a slightly yellow solid, mp 131–134 °C. This was recrystallized twice from hexane/tetrahydrofuran and once from carbon tetrachloride to yield 4.19 g (82%) of a white powdery solid: mp 135–136 °C; IR (KBr) 3300–2500 (br, s), 1700 (s), 1573 (m), 1468 (s), 1440 (s), 1410 (s), 1360 (m), 1342 (m), 1335 (m), 1305 (m), 1255 (s), 1238 (s), 1192 (m), 1185 (m), 1105 (s), 1090 (s), 1082 (s), 1060 (m), 1040 (s), 1012 (m), 975 (m), 965 (m), 935 (m), 860 (m), 835 (m), 800 (w), 770 (m), 748 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.67–2.13 (m, 1 H), 2.4–3.2 (m, 4 H), 3.33 (s, 3 H), 3.78 (s, 6 H), 4.63 (distorted t, $J$ = 3 Hz, 1 H), 6.9 (s, 1 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$ = 0) $\delta$ 180.46 (s in off-resonance), 154.53 (s), 148.51 (s), 132.15 (s), 125.21 (s), 116.66 (s), 113.07 (d), 69.86 (d), 60.49 (q), 56.46 (q), 56.07 (q), 35.54 (d), 28.45 (t), 24.47 ppm (q). The analytical sample was recrystallized from carbon tetrachloride; mp 135–136 °C. Anal. ($C_{14}H_{17}O_5Br$): C, H.

**17b.** To a slurry of 2.34 g (6.78 mmol) of **15d** in 40 mL of ether was added a solution of diazomethane in ether until the solution turned yellow. Removal of the excess diazomethane and workup gave 2.21 g (91%) of a slightly yellow crystalline solid, mp 88–91 °C. One recrystallization from hexane yielded 1.96 g (81%) of colorless needles: mp 91.5–93 °C; IR (KBr) 3000 (m), 2980 (m), 2950 (m), 2890 (m), 2820 (m), 1720 (s), 1572 (m), 1473 (s), 1440 (m), 1410 (m), 1375 (m), 1305 (m), 1236 (s), 1210 (s), 1180 (s), 1110 (s), 1090 (s), 1040 (s), 1015 (m), 1005 (m), 975 (m), 965 (m), 860 (m), 848 (m), 775 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.6–2.13 (m, 1 H), 2.4–3.47 (m, 4 H), 3.33 (s, 3 H), 3.65, 3.67, 3.8 (s, 9 H), 4.55 (distorted t, $J$ = 6 Hz, 1 H), 6.9 (s, 1 H); $^{13}C$ NMR ($CDCl_3$, $Me_4Si$ = 0, proton decoupled) $\delta$ 175.12 (singlet in off-resonance), 154.63 (s), 148.56 (s), 132.34 (s), 125.21 (s), 116.57 (s), 112.97 (d), 69.96 (d), 60.44 (q), 56.61 (q), 56.07 (q), 51.61 (q), 35.30 (dd), 28.50 (t), 24.91 (t); exact mass calcd for $C_{15}H_{19}O_5Br$ $m/e$ 358.041 62, found $m/e$ 358.042 21 (difference $m/e$ 0.0006). Anal. ($C_{15}H_{19}O_5Br$): C, H.

**18b.** To a mechanically stirred solution of 14.7 mL of lithium cyclohexylisopropylamide in 80 mL of tetrahydrofuran at −70 °C under nitrogen was added a solution of 4.8 g (13.4 mmol) of **17a**/**17b** (~80:20) in 12 mL of tetrahydrofuran. The mixture was stirred at −70 °C for 1 h, and then 9.12 g (18.7 mmol) of $MoO_5$·HMPA·Py was added;[20] the solution was stirred at −65 °C for 1.5 h and finally allowed to warm to room temperature. After the reaction was quenched with 30 mL of saturated sodium sulfite, workup as described (vida supra), followed by trituration of the crude product with E/H, gave 3.55 g of yellow solid which was primarily a mixture of **18a** and **18b**. Chromatography of this material on silica gel (56 g; 40 × 2 cm column) proceeded as follows: 200 mL of 10% E/H, unidentified impurities; 200 mL of 20% E/H, 0.2 g of impure starting ester; 200 mL of 30% E/H, nil; 200 mL of 40% E/H, nil; 200 mL of 45% E/H and 200 mL of 50% E/H, 3.8 g (75%) of **18b**. Recrystallization from hexane/dichloromethane gave pure **18b**: 57%; mp 115.5–117 °C; IR (KBr) 3435 (s), 2950 (m), 2925 (m), 1737 (s), 1572 (m), 1462 (s), 1405 (s), 1367 (m), 1305 (m), 1262 (m), 1236 (s), 1220 (s), 1115 (s), 1085 (s), 1070 (m), 1060 (m), 1047 (s), 1020 (m), 965 (m), 840 (m), 795 (m), 775 (m) $cm^{-1}$. Anal. ($C_{15}H_{19}O_6Br$): C, H.

**19a,b.** To a mechanically stirred mixture of tetrahydrofuran (30 mL) and dimethyl sulfoxide (9.6 mL) under nitrogen at 0 °C was added 12.6 mL (20.1 mmol) of a solution of methyllithium/lithium bromide complex in ether (1.6 M) over 5 min, and the mixture was stirred for 10 min. To the white slurry was added a solution of 2.4 g (6.4 mmol) of **18a** and **18b** in 10 mL of tetrahydrofuran all at once, and the mixture was stirred at 0 °C for 2 h and at room temperature for 2 h. The reaction was quenched with methanol, and the solvents were removed in vacuo. The residue was dissolved in 100 mL of dichloromethane, and 5% hydrochloric acid was added with shaking until the pH was 2. The layers were separated, and the aqueous layer was further extracted with 20 mL of dichloromethane. Workup followed by trituration with dichloromethane and ether and then drying afforded 2.67 g (100%) of a yellow powder identified to be the $\beta$-keto sulfoxide from its infrared spectrum: IR (KBr) 3400 (br, m), 2935 (m), 1707 (s), 1575 (m), 1470 (s), 1435 (m), 1405 (s), 1365 (m), 1310 (m), 1235 (s), 1190 (m), 1095 (s), 1055 (s), 1015 (s), 960 (m), 830 (w), 755 (s) $cm^{-1}$. The material was dissolved in a mixture of tetrahydrofuran (126 mL) and water (13.8 mL) and reduced with aluminum amalgam prepared from 2.07 g of aluminum foil. After 1.5 h the solution was suction filtered and the solid washed with methylene chloride. The filtrate was concentrated and extracted with 150 mL of methylene chloride. Workup gave 1.82 g of gummy material which was chromatographed on 50 g of silica gel (2.5 × 30 cm). Elution proceeded as follows: 200 mL of 20% E/H, 0.25 g of unidentified impurities; 200 mL of 30% E/H, unidentified impurity; 200 mL of 35% E/H and 100 mL of 40% E/H, 0.17 g (7%) of **19a** [mp 68–71 °C; IR (KBr) 3400–3440 (br, m), 2940 (m), 1710 (s), 1573 (m), 1475 (s), 1447 (m), 1410 (m), 1355 (m), 1243 (s), 1120 (m), 1100 (s), 1070 (s) $cm^{-1}$; exact mass calcd for $C_{15}H_{19}O_5Br$ $m/e$ 358.041 62, found $m/e$ 358.042 27 (difference $m/e$ 0.0007)].

Elution was continued as follows: 300 mL of 40% E/H, 200 mL of 45% E/H, and 100 mL of 50% E/H, 1.25 g (55%) of **19b** [mp 79–80 °C; IR (KBr) 3440 (br, m), 2915 (m), 1721 (s), 1575 (m), 1470 (s), 1405 (s), 1364 (m), 1345 (m), 1320 (m), 1301 (m), 1230 (s), 1108 (s), 1086 (s), 1056 (m), 1040 (s), 1020 (m) $cm^{-1}$]. Anal. ($C_{15}H_{19}O_5Br$): C, H.

**Conversion of 14 to 19a and 19b without Purification of Intermediates.** A slurry of 13.6 g (41.1 mmol) of **14** in 326 mL of absolute ethanol maintained under an argon atmosphere was treated with 4.8 g (128 mmol) of sodium borohydride at −25 °C. After warming to −15 °C, the mixture was stirred for 2 h and was then warmed to 5 °C. After 1 h the mixture was warmed to room temperature and diluted with 90 mL of water. Most of the ethanol was removed in vacuo at an elevated temperature (50–60 °C), and the residue was dissolved into 240 mL of water. The aqueous solution was extracted with chloroform (60 mL) and ether (30 mL). The aqueous phase was cooled to 5 °C and carefully acidified with rapid stirring to pH 2 by using 25% sulfuric acid solution, upon which an oil separated and slowly solidified over 1 h. The solid was vacuum filtered, and the filter cake was washed with

cold water. Vacuum drying of the solid afforded 13.0 g (95%) of crude **15a** and **15b**, mp 151–154 °C.

To a mixture of 380 mL of dry tetrahydrofuran and 2.16 g (90.3 mmol) of hexane-washed sodium hydride under nitrogen was added 13.0 g (39.3 mmol) of a mixture of *cis*- and *trans*-hydroxy acids **15a,b** and the solution heated to reflux for 2 h. The mixture was cooled, 8.35 g (59 mmol) of methyl iodide was added, and the slurry was heated in a bath at 40–45 °C overnight. The solvent was removed in vacuo, and the residue was dissolved in water (200 mL) and extracted with ether (2 × 50 mL). The aqueous layer was cooled in ice and carefully acidified to pH 2 by using 5% sulfuric acid to yield a thick yellow liquid which solidified on addition of 20 g of salt and cooling for 1 h in ice. The solid was filtered, washed, and dried in vacuo to yield 12.63 g (93%) of a slightly yellow solid which was recrystallized once from carbon tetrachloride to yield 11.64 g (86%) of a slightly yellow crystalline solid. To a slurry of the mixture of methoxy acids **15c,d** in ether (150 mL) was added a solution of diazomethane in ether until the solution was distinctly yellow. After 5 min, the excess diazomethane and the solvent were evaporated, and the residue was dissolved in 150 mL of ether. The solution was washed with 5% bicarbonate solution (2 × 30 mL) and saturated brine solution (40 mL), dried with calcium sulfate, and concentrated to yield 11.3 g (95%) of a crystalline solid. One recrystallization from hexane yielded 10.84 g (91%) of a mixture of *cis*- and *trans*-methoxy esters **17a,b**.

In a three-necked flask equipped with a mechanical stirrer, gas inlet, and low-temperature thermometer, a solution of isopropylcyclohexylamine (2.55 mL, 15.5 mmol) in dry tetrahydrofuran (70 mL) maintained under a dry argon atmosphere was treated with 1.66 M *n*-butyllithium (8.36 mL, 15.5 mmol) in hexane at −65 °C. After 25 min, a solution of 4.65 g (12.9 mmol) of **17a,b** in dry tetrahydrofuran (25 mL) was added at such a rate as to keep the reaction temperature below −60 °C. After the addition was complete (30 min), 8.43 g (19.4 mmol) of MoOPH was added through the top of the flask, and the resulting slurry was stirred at −65 °C for 1.5 h. The mixture was allowed to warm to room temperature over 0.5 h and was then quenched with 30 mL of a saturated sodium sulfite solution. The two layers of the reaction mixture were separated, and the aqueous phase was extracted with 30 mL of ether. This organic phase, combined with the organic phase of the reaction mixture, was concentrated in vacuo. The residue was dissolved into dichloromethane (25 mL) and ether (100 mL). The resulting solution was extracted with 5% hydrochloric acid solution (2 × 25 mL), 5% sodium carbonate solution (2 × 25 mL), and saturated salt solution (1 × 25 mL). Drying and concentration gave 4.4 g of a green-yellow oil which upon addition of ether and hexane gave, with the aid of a seed crystal, 3.54 g (73%) of crude **18a,b** as an off-white solid. This material was suitable for further use.

A mechanically stirred solution of dry dimethyl sulfoxide (23.3 mL) in dry tetrahydrofuran (75 mL) maintained under an argon atmosphere was treated with 30.6 mL (48.8 mmol) of a 1.6 M methyllithium–lithium bromide complex in ether at 0 °C. The resulting white slurry was then treated with a solution of 6.0 g (~46.5 mmol) of crude (>90% pure) **18a,b** in 24 mL of dry tetrahydrofuran. After the reaction mixture was stirred at 0 °C for 2 h, it was quenched with methanol (10 mL) and concentrated in vacuo. The residue was disssolved into dichloromethane (100 mL), and the resulting solution was shaken with 5% hydrochloric acid solution. The layers were separated, and the organic phase was shaken with more 5% hydrochloric acid solution. This process was repeated until the aqueous layer was pH 2. The combined aqueous phases were extracted with dichloromethane (20 mL), and this organic phase was combined with the organic phase from above. The combined organic phases were washed with water (100 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to afford 6.9 g of a light yellow foam. A solution of this foam in tetrahydrofuran (315 mL) and water (34.5 mL) was treated at 25 °C with aluminum amalgam prepared from 4.38 g (10 equiv) of aluminum foil. After 1.5 h the mixture was vacuum filtered, and the filter cake was washed with ether (100 mL). The combined filtrate and ether washing were concentrated in vacuo, and the residue was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to give 5.2 g of a yellow oil. This oil was coated onto 5.5 g of silica gel, and this was applied to the top of a silica gel column (143 g, 3.4 × 34 cm). Elution proceeded as follows: 400 mL of 20% E/H, unknown amount of impurity; 400 mL of 30% E/H, nil; 700 mL of 40% E/H, 1.14 g of a mixture of **19a** and impurities; 300 mL of 40% E/H, unknown amount of impurity; 800 mL of 50% E/H, 2.17 g (38%) of **19b**. The impure **19a** was further chromatographed on a Lobar prepacked column [Li Chroprep Si 60 (40–63 um) silica gel] with 40% E/H to afford 0.475 g (8%) of **9a** and 0.508 g of unidentified material. This comprises overall yields of 20% (**19b**) and 4% (**19a**) from **14**. Smaller runs gave slightly higher yields: 32% vs. 24% overall.

**11b.** A solution of **19b** (1.0 g, 2.8 mmol) in dry ethylene glycol (6 mL) and trimethyl orthoformate (3 mL) under $N_2$ was treated with 60 mg of *p*-toluenesulfonic acid at 0 °C. After 76 min at 0 °C, the reaction mixture was quenched with a solution of 20% potassium hydroxide (5 mL) and methanol (5 mL). This mixture was allowed to warm to room temperature and was stirred for 2 h. During this period a white solid precipitated from solution. After addition of 1.0 g of sodium chloride, cooling of the mixture to 0 °C, and stirring for an additional 1 h, the solid was then filtered from the cold mixture and was washed with 10 mL of cold water. Drying in vacuo gave 0.856 g (76.4%) of a white solid (mp 96–101 °C) which was used without further purification. The analytical sample, recrystallized from hexane/methylene chloride, had the following: mp 105–106 °C; IR (KBr) 3420 (s), 1570 (m), 1470 (s), 1435 (m), 1405 (m), 1371 (m), 1340 (m), 1292 (m), 1230 (s), 1219 (m), 1190 (m), 1099 (vs), 1080 (vs), 1040 (s), 1030 (s), 910 (m) $cm^{-1}$. Anal. ($C_{17}H_{25}O_6Br$): C, H.

**12b.** Into the anode compartment of a divided cell was placed **11b** (1.0 g, 2.5 mmol), dry tetrahydrofuran (10 mL), and 3.1% methanolic potassium hydroxide solution (50 mL). The cathode compartment was filled with 60 mL of a 2.6% methanolic potassium hydroxide solution. The material was electrolyzed in the potential range 1.4–1.65 V relative to a Pt reference electrode and in a temperature range of 0–10 °C until the UV absorption peak of the starting material at 290 nm had decreased to approximately 5% of its initial value (4 h). The contents of the anode compartment were treated with dry ice chips until the pH of the solution was near 9. The solution was concentrated in vacuo at room temperature, and the residue was treated with 30 mL of water. This mixture was extracted with dichloromethane (3 × 10 mL) and worked up to afford 1.09 g of an oily solid which when triturated with hexane gave 0.887 g (77%) of **12b**. Workup of the solution in the cathode side of the cell in a fashion similar to that for the anode side afforded another 0.049 g of **12b**. The total yield of **12b** was 0.936 g (81%): mp 190–191 °C (E/H); IR (KBr) 3460 (m), 1220 (m), 1190 (m), 1090 (vs, br), 1055 (m), 1045 (m), 1010 (m) $cm^{-1}$; $^1H$ NMR 6.67 (s, 1 H), 4.40–3.94 (partially buried m, 1 H), 4.03 (s, 4 H), 3.41 (s, 3 H), 3.30 (s, 6 H), 3.17 (s, 6 H), 2.50–2.28 (m, 2 H), 2.20–1.68 (m, 3 H), 1.39 (s, 3 H). Anal. ($C_{19}H_{29}O_8Br$): C, H.

**32b.** A mechanically stirred solution of **12b** (1.204 g, 2.59 mmol) in dry tetrahydrofuran (30 mL) maintained under a dry argon atmosphere was treated with 1.39 M *n*-butyllithium in pentane solution (3.90 mL, 5.43 mmol) at −80 °C. After 5 min, a solution of 0.684 g (3.88 mmol) of benzocyclobutenedione monoketal **6** in 5 mL of dry tetrahydrofuran was added to this mixture via a syringe. The reaction mixture was stirred at −70 °C for 0.5 h and was allowed to warm to room temperature over 0.5 h. The mixture was heated to reflux for 3 h and was concentrated in vacuo. The residue was diluted with water (30 mL) and was extracted with chloroform (4 × 10 mL). Workup gave 1.89 g of an orange-brown oil which was dissolved in a mixture of tetrahydrofuran (27.3 mL), water (10.9 mL), and concentrated hydrochloric acid (3.6 mL) at room temperature. After 40 h the mixture was concentrated in vacuo, and the residue was extracted with chloroform (3 × 10 mL). Workup gave an orange gum which crystallized from methanol to give 0.662 g (62%) of **32b** as an orange solid in two crops; mp 185–187 °C. The yield of product in several runs was 55–65%. A portion of this material was recrystallized from methanol; mp 191–192 °C (lit.[23] mp 190–192 °C).

**33b.** A mechanically stirred solution of 0.90 g (2.2 mmol) of **32b** in dry dichloromethane (108 mL) maintained under a dry argon atmosphere was treated with 15.4 mL (15.4 mmol) of a 1 M boron trichloride in dichloromethane solution at −65 °C. The addition of the boron trichloride was effected over 5–10 min so

as to keep the reaction temperature as close to −65 °C as possible. After stirring the mixture for 0.5 h, it was treated with 7 mL of dry methanol and allowed to warm to room temperature. The mixture was concentrated in vacuo to give 0.993 g (> 100%) of **33b** as a red solid. This material is pure enough for further use with no additional purification. Recrystallization from hexane/methylene chloride gave analytically pure material as a bright-red solid: mp 202–204 °C; IR (KBr) 3420 (br, s), 1705 (m), 1625 (s), 1585 (s), 1415 (s), 1375 (s), 1345 (m), 1280 (m), 1240 (m), 1075 (s) $cm^{-1}$; exact mass for $C_{21}H_{18}O_7$ calcd $m/e$ 382.1052, found $m/e$ 382.1057 (difference $m/e$ 0.0005).

**34a from 34b.** A single-necked, round-bottomed flask equipped with a magnetic stirring bar and containing 12 mL of trifluoroacetic acid maintained under a dry argon atmosphere was cooled in a dry ice/2-propanol bath until the acid formed a slush. To the acid slush was added 0.290 g (0.787 mmol) of **34b** through the top of the flask. The red solution was allowed to slowly warm to room temperature (ca. 0.5 h) and was stirred at that temperature for 25 h. Concentration of the reaction mixture under high vacuum at room temperature afforded a red solid. This solid was dissolved into 29 mL of acetone and was treated with 12 mL of a freshly prepared 5% sodium bicarbonate solution. After 1 h the reaction mixture was diluted with 60 mL of water and was exhaustively extracted with chloroform (total of 100 mL). This material was combined with that of a similar experiment to give 0.599 g of a red foam. This foam was chromatographed on 120 g of silica gel (3.2 × 40 cm) with 20% ethyl acetate/toluene as the eluant (20-mL fractions). Elution proceeded as follows: 140 mL, nil; 1100 mL, 0.101 g of a mixture of at least three impurities; 1000 mL, 0.188 g (39%) of pure **34a**, mp 183–185 °C (lit.[6] 184–186 °C); 180 mL, 0.025 g (5%) of a mixture of **34a** and **34b**; 2000 mL, 0.131 g (27%) of pure **34b**.

**34a.** A single-necked, round-bottomed flask equipped with magnetic stirring bar and containing 24 mL of trifluoroacetic acid maintained under a dry argon atmosphere was cooled in a dry ice/2-propanol bath until the acid formed a slush. Then 0.60 g (ca. 1.6 mmol) of **33b** was added through the top of the flask. The red solution was allowed to slowly warm to room temperature (ca. 0.5 h) and was stirred at that temperature for 21 h. Concentration of the reaction mixture under high vacuum at room temperature afforded a red foam. This foam was dissolved in acetone (60 mL) and treated with freshly prepared 5% sodium bicarbonate solution (24 mL). After 1 h the mixture was diluted with water (100 mL) and was then exhaustively extracted with chloroform (total of 200 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo to afford 0.681 g of a red foam. In the series of reactions **32b** → **33b** → **34a,b**, 1.51 g (4.6 mmol) of pure **32b** yielded 1.55 g of crude **33b** which was used without purification in the next step. This afforded a total of 1.62 g of crude material which by TLC appeared to be a mixture of **34a**, **34b**, and a totally aromatic compound. This crude material was roughly divided in half, and each portion was chromatographed on silica gel. The first portion, 0.788 g, was chromatographed on 150 g of silica gel (3.2 × 50 cm) with 10% ethyl acetate/toluene as the eluant (20-mL fractions). Elution proceeded as follows: 160 mL, nil; 320 mL, 0.055 g (9%) of aromatized material; 940 mL, 0.041 g of at least two impurities; 920 mL, 0.092 g (13%) of recovered **33b**; 100 mL, 0.004 g of a mixture of **33b** and **34a**; 1480 mL, 0.208 g (31%) of pure **34a**; 160 mL, 0.016 g (2%) of a mixture of **34a** and **34b**; 1960 mL, 0.148 g (22%) of pure **34b**. For the two runs, there was collected 0.090 g (7%) of aromatized compound, 0.216 g (15%) of recovered pure **33b**, 0.445 g (33%) of pure **34a**, and 0.300 g (22%) of pure **34b**.

**11a.** A solution of 0.30 g (0.84 mmol) of **19a** in 1.8 mL of dry ethylene glycol and 0.90 mL of dry trimethyl orthoformate maintained under a dry argon atmosphere was treated with 18 mg of anhydrous *p*-toluenesulfonic acid at 25 °C. After 10 min the reaction mixture was quenched with 2 mL of a 1:1 20% sodium hydroxide/methanol solution and was stirred at room temperature for 2 h. The reaction mixture was diluted with 100 mL of water and continuously extracted with ether. The ether extract was dried over anhydrous sodium sulfate and concentrated to give 0.394 g of a colorless oil. Chromatography of this oil on 32 g of activity III neutral alumina (2 × 13 cm) with 5% ethyl acetate/benzene as the eluent proceeded as follows: 25 mL, nil; 20 mL, 0.062 g of a mixture of impurities; 165 mL, 0.188 g (56%) of **11a** as a white solid, mp 81–83 °C. Recrystallization of this solid from hexane afforded the analytical sample: mp 83–85 °C; IR (KBr) 3440 (m), 2940 (w), 1578 (m), 1468 (s), 1435 (w), 1405 (m), 1383 (m), 1325 (m), 1310 (w), 1228 (s), 1176 (m), 1087 (s), 1056 (m), 1035 (s), 1020 (s), 955 (w), 895 (m), 822 (w), 764 (w) $cm^{-1}$. Anal. ($C_{17}H_{25}O_6Br$): C, H.

**12a.** Into the anode compartment of a divided cell was placed a solution of 0.425 g (0.95 mmol) of **11a** in 60 mL of a 2.0% potassium hydroxide/methanol solution. The cathode compartment was also filled with a 2.0% potassium hydroxide/methanol solution. Electrolysis was carried out at a potential of 1.5–1.65 V and at 0–10 °C until the UV absorption at 290 nm had decreased to about 5% of its initial value (3 h). The contents of the anode compartment were treated with solid carbon dioxide until the solution was only slightly basic, and the solution was then concentrated in vacuo at room temperature. The residue was diluted with 30 mL of water and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over anhydrous calcium sulfate and concentrated in vacuo to afford 0.320 g of an oily yellow solid. Trituration with ether/hexane at low temperature yielded 0.283 g (58%) of **12a** as an off-white solid which was utilized in the next step: mp 144–149 °C; IR (KBr) 3440 (s), 2940 (s), 2815 (w), 1450 (m), 1375 (m), 1315 (m), 1210 (s), 1180 (s), 1085 (vs), 970 (m), 900 (m), 720 (m) $cm^{-1}$; $^1H$ NMR $\delta$ 6.7 (s, 1 H), 4.9 (s, 1 H), 4.25–4.15 (m, 1 H), 4.05–3.85 (s, 4 H), 3.45 (s, 3 H), 3.3 (s, 3 H), 3.25 (s, 3 H), 3.15 (s, 3 H), 3.05 (s, 3 H), 2.7–2.2 (partially resolved AB, 2 H), 1.75–1.2 (partially buried m, 2 H), 1.4 (s, 3 H).

**32a.** A solution of 0.10 g (0.22 mmol) of **11a** in 6 mL of dry tetrahydrofuran maintained under an argon atmosphere was treated with 0.272 mL (9.45 mmol) of a 1.66 M *n*-butyllithium in hexane solution at −80 °C. After 5 min a solution of 0.042 g (0.24 mmol) of benzocyclobutenedione monoketal in 0.5 mL of dry tetrahydrofuran was added, and the resulting mixture was stirred at −70 °C for 0.5 h. The reaction mixture was allowed to warm to room temperature over 0.5 h and was then heated to reflux for 3 h. The mixture was concentrated in vacuo, and the residue was diluted with 30 mL of water and extracted with dichloromethane (3 × 8 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated to give 0.177 g of a light yellow oil. This oil was dissolved in a mixture of 6.5 mL of tetrahydrofuran, 2.6 mL of water, and 0.87 mL of concentrated hydrochloric acid at room temperature. After 43 h the mixture was concentrated in vacuo, and the residue was extracted with dichloromethane (3 × 8 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in vacuo, yielding a brown oil. Addition of methanol to this oil with cooling afforded 0.039 g (44%) of **32a** as an orange-yellow solid in two crops. A portion of this material was recrystallized from dichloromethane/methanol, yielding orange needles: mp 187.5–190 °C; IR (KBr) 3420 (br, s), 2940 (m), 1715 (m), 1670 (s), 1595 (m), 1460 (m), 1335 (m), 1320 (m), 1260 (m), 1230 (m), 1205 (m), 1070 (m), 1040 (m), 990 (m) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.20 (m, 2 H), 7.75 (m, 2 H), 5.00 (s, 1 H), 4.93 (dd, $J$ = 3.5, 2.2 Hz, 1 H), 4.00 (s, 3 H), 3.91 (s, 3 H), 3.59 (s, 3 H), 3.28 (dd, $J$ = 18.4, 1.8 Hz, 1 H), 3.05 (d, $J$ = 18.4 Hz, 1 H), 2.45 (incompletely resolved t of d, $J$ = 14.9, ~3.0, ~2.0 Hz, 1 H), 2.43 (s, 3 H), 1.90 (dd, $J$ = 14.9, 3.4 Hz, 1 H); exact mass calcd for $C_{23}H_{22}O_7$ $m/e$ 410.136 540, found $m/e$ 410.137 222 (difference $m/e$ 0.000 682).

**35.** A magnetically stirred solution of **12b** (0.60 g, 1.3 mmol) in dry tetrahydrofuran (16 mL) maintained under a dry $N_2$ atmosphere was treated with a 1.52 M *n*-butyllithium in pentane solution (1.78 mL, 2.70 mmol) at −80 °C. After 10 min a solution of **21** (0.93 g, 1.7 mmol) in dry tetrahydrofuran (2.5 mL) was added to this mixture via syringe. The reaction mixture was then allowed to warm to room temperature over 1 h. The mixture was heated to reflux for 3 h and then cooled and concentrated in vacuo. The residue was diluted with water and extracted with dichloromethane (5 × 10 mL). Workup gave 0.94 g of a yellow foam which was dissolved in a mixture of tetrahydrofuran (20 mL), water (8 mL), and concentrated hydrochloric acid (2.6 mL) at room temperature. After 48 h the mixture was concentrated in vacuo, and the residue was extracted with dichloromethane (5 × 10 mL). The workup gave an orange-yellow foam which crystallized from methanol to give 0.272 g of **35**, mp 164–167 °C. The mother liquor

(0.32 g) was chromatographed on silica gel (30 g) with 0.5–1.0% methanol/dichloromethane as the eluant, yielding an additional 46 mg of **35** for a total yield of 0.32 g (56%). A portion of this material was recrystallized twice from methanol: mp 166–168.5 °C; IR (KBr) 3460 (s, br), 1710 (m), 1675 (s), 1585 (m), 1450 (m), 1400 (m), 1330 (m), 1315 (m), 1265 (s), 1230 (m), 1210 (m), 1100 (m), 1075 (m), 1030 (m), 1015 (m) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.75 (dd, $J$ = 7.6, 1.1 Hz, 1 H), 7.63 (dd, $J$ = 8.1, 7.6 Hz, 1 H), 7.25 (dd, $J$ = 8.1, 1.1 Hz, 1 H), 5.00 (dd, $J \simeq$ 4.0, 2.6 Hz, 1 H), 4.01 (s, 3 H), 3.99 (s, 3 H), 3.93 (s, 3 H), 3.49 (br s, 1 H), 3.29 (s, 3 H), 3.22 (d, $J$ = 15.3 Hz, 1 H), 3.02 (dd, $J$ = 15.4, 1.1 Hz, 1 H), 2.66 (dd, $J$ = 15.2, 2.9 Hz, 1 H), 2.40 (s, 3 H), 1.91 (dd, $J$ = 15.4 ~4.0 Hz, 1 H); exact mass calcd for $C_{24}H_{24}O_8$ $m/e$ 440.147 103, found $m/e$ 440.148 340 (difference $m/e$ 0.001 237).

**29a.** A mixture of 2.6 g (14.6 mmol) of **28a**, 200 mL of benzene, 2.4 mL of ethylene glycol, and 100 mg of $p$-toluenesulfonic acid was heated to reflux for 60 h with azeotropic removal of water. The solution was cooled and poured into 2% potassium hydroxide. Workup yielded 3.14 g (99%) of a clear oil which was a 9:1 mixture of **29a** and **28a**. While this material was suitable for use without purification, pure **29a** can be obtained by chromatography on Fluorisil with 15% ether/hexane as the eluant. The ketal shows IR (neat) 1238 (s), 1160 (m), 970 (s), 870 (sh), 840 (s), 750 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 0.05 (s, 9 H), 3.3 (s, 1 H), 4.05 (s, 4 H), 6.9–7.3 (m, 4 H); exact mass calcd for $C_{13}H_{18}O_2Si$ $m/e$ 234.107 600, found $m/e$ 234.108 329 (difference $m/e$ 0.0007).

**30a.** A mixture of 1.0 g (4.3 mmol) of **29a**, 0.85 g (4.7 mmol) of $N$-bromosuccinimide, and 40 mL of carbon tetrachloride was heated to reflux under illumination with a 200-W unfrosted incandescent bulb. After 30 min the reaction was judged complete. The cooled reaction mixture was poured into 50 mL of cold 5% sodium bicarbonate solution. Extraction with carbon tetrachloride (2 × 25 mL) and a conventional workup gave a light tan solid. The material can be obtained pure by careful crystallization from hexane/ether at −70° C. However, the high solubility of the crude product makes this operation tedious. Rapid chromatography on Fluorisil with 1% ether/hexane as the eluant gave 0.98 g (73%) of **30a**: mp 85–87 °C; IR (KBr) 2955 (m), 2900 (m), 1340 (s), 1275 (m), 1250 (s), 1220 (m), 1170 (s), 1118 (m), 1070 (s), 1040 (s), 1018 (m) 1000 (m), 950 (s), 838 (s), 752 (s) $cm^{-1}$; $^1H$ NMR 0.05 (s, 9 H), 3.8–4.3 (m, 4 H), 7.1–7.5 (m, 4 H); exact mass calcd for $C_{13}H_{17}BrO_2Si$ $m/e$ 312.018 165, found $m/e$ 312.019 025 (difference $m/e$ 0.000 86).

**6.** To a dry flask equipped with a magnetic stirrer and a nitrogen inlet were added 0.75 mL of dry dimethyl sulfoxide and 48 mg (0.24 mmol) of silver tetrafluoroborate. The mixture was heated to 50 °C and treated with 50 mg (0.16 mmol) of **30a**. After 6 h at 50 °C the mixture was cooled to room temperature and treated with 24 mg (0.26 mmol) of potassium fluoride dihydride. After being stirred for 1 h, the dark brown mixture was filtered through a Celite pad, and the filter pad was washed with 5 mL of methylene chloride. The combined filtrate and washes were extracted with water (3 × 5 mL), washed with brine, and dried by being passed through a cone of calcium sulfate. Removal of solvent gave 24 mg (85%) of off-white crystals which were identical with an authentic sample; mp 108–111 °C (lit.[11c] mp 109–112 °C).

**29b.** To a dry flask equipped with a magnetic stirrer and under static nitrogen pressure were added 0.5 g (2.3 mmol) of **28b**, 2.5 mL of trimethyl orthoformate, 5 mL of ethylene glycol, and 50 mg of $p$-toluenesulfonic acid. After being stirred for 26 h at 23 °C, the mixture was cooled to 0 °C and treated with 5 mL of 5% aqueous sodium hydroxide and 2.5 mL of methanol. After being stirred for 3 h at 0 °C, the mixture was filtered, yielding a white solid which was washed with 5 mL of ice-cold water. Drying under vacuum yielded 0.44 g (73%) of white crystals (mp 63–66 °C) which were utilized without further purification. Recrystallization from ether/hexane gave the following: mp 68–70 °C; IR ($CCl_4$) 2960 (m), 2890 (m), 1605 (m), 1587 (m), 1480 (s), 1440 (m), 1290 (s), 1275 (s), 1250 (s), 1220 (m), 1150 (w), 1088 (m), 1080 (m), 1065 (s), 1040 (w), 980 (s), 950 (w), 865 (s), 845 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.00 (s, 9 H), 3.17 (s, 1 H), 3.80 (s, 3 H), 3.80–4.25 (m, 4 H), 6.6 (2 br s, 2 H), 7.2 (dd, $J_1$ = 8, $J_2$ = 8 Hz, 1 H); exact mass calcd for $C_{15}H_{20}O_3Si$ $m/e$ 264.118 163, found $m/e$ 264.119 094 (difference 0.000 830).

**30b.** To a dry flask equipped with magnetic stirrer, condenser, and nitrogen inlet were added 0.4 g (1.5 mmol) of **29b**, 0.3 g (1.7 mmol) of $N$-bromosuccinimide, and 16 mL of carbon tetrachloride under static nitrogen pressure. The reaction mixture was heated to 60 °C and illuminated with a 200-W unfrosted incandescent bulb. After 20 min the light was removed, and the mixture was cooled to 25 °C. The reaction mixture was poured into 20 mL of a cold aqueous sodium bicarbonate solution, and the layers were separated. The aqueous layer was extracted with carbon tetrachloride (2 × 10 mL) and worked up to yield 0.50 g (96%) of a light yellow solid (mp 88–94 °C) which was used without further purification. Recrystallization from ether/hexane gave white needles: mp 97–99 °C; IR (KBr) 2980 (m), 2945 (m), 2895 (m), 1608 (s), 1584 (s), 1482 (s), 1434 (s), 1355 (m), 1375 (s), 1265 (s), 1245 (s), 1215 (s), 1184 (m), 1090 (s), 1067 (s), 1040 (s), 1015 (m), 1000 (w), 950 (m), 925 (m), 885 (m) 865 (s), 845 (s), 818 (s), 772 (s), 760 (m), 732 (s), 696 (m), 620 (w) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.05 (s, 9 H), 3.75 (s, 3 H), 3.7–4.3 (m, 4 H), 6.73 (d, $J$ = 6 Hz, 1 H), 6.8 (d, $J$ = 6 Hz, 1 H), 7.3 (t, $J$ = 6 Hz, 1 H); exact mass calcd for $C_{14}H_{19}O_3BrSi$: $m/e$ 342.0287, found 342.0296 (difference $m/e$ 0.0009).

**21.** To a dry flask equipped with magnetic stirrer and nitrogen inlet were added 10 mL of dry dimethyl sulfoxide and 0.93 g (4.6 mmol) of silver tetrafluoroborate. The mixture was heated to 60 °C and treated with 0.787 g (2.32 mmol) of **30b**. After 16 h at 60 °C the mixture was cooled to room temperature and treated with 0.32 g (3.4 mmol) of potassium fluoride dihydrate. After being stirred for 1 h, the dark brown mixture was filtered through a Celite pad, and the filter pad was washed with 50 mL of methylene chloride. The combined filtrate and washes were extracted with water (3 × 50 mL), washed with brine, and dried through calcium sulfate. Removal of the solvent yielded 0.402 g (85%) of light yellow crystals, mp 78–81 °C. An analytical sample was prepared by sublimation, yielding white crystals: mp 81–83 °C; IR (KBr) 2895 (m), 1762 (vs), 1597 (m), 1490 (m), 1482 (s), 1435 (m), 1350 (m), 1295 (s), 1245 (m), 1216 (m), 1180 (m), 1040 (s), 1010 (m), 940 (m), 840 (m), 800 (m), 748 (s) $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 3.98 (s, 3 H), 4.1–4.3 (m, 4 H), 7.08 (d, $J$ = 6 Hz, 1 H), 7.18 (d, $J$ = 6 Hz, 1 H), 7.5 (t, $J$ = 6 Hz, 1 H). Anal. ($C_{11}H_{10}O_4$): C, H.

**3b.** A solution of **2** (100 mg, 0.76 mmol) and ethanedithiol (72 mg, 0.76 mmol) in dichloromethane (5 mL) containing ca. 100 mg of calcium sulfate was treated with boron trifluoride etherate (50 $\mu$L) and the mixture stirred for 24 h. The mixture was then filtered, and the filtrate was washed with sodium bicarbonate (10 mL) and then worked up to afford an oily solid. Sublimation [60 °C (0.01 mm)] gave 116 mg (74%) of **3b** as light yellow crystals, mp 84–87 °C. Recrystallization from ether/hexane gave yellow crystals: mp 87.5–89.0 °C; IR (KBr) 2915 (m), 1775 (vs), 1735 (m), 1680 (m), 1460 (m), 1415 (m), 1270 (m), 1135 (m), 1080 (m), 860 (s), 840 (m), 755 (s), 680 (m), 630 (m) $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 3.55 (s, 4 H), 7.2–7.8 (m, 4 H). Anal. ($C_{10}H_8OS_2$): C, H.

**3c.** By a procedure analogous to that for **3b**, 100 mg of **2** yielded 130 mg (77%) of **3c**: mp 124–127 °C (softens at 110 °C); IR (KBr) 2905 (m), 1755 (vs), 1580 (s), 1460 (m), 1420 (m), 1410 (m), 1330 (m), 1270 (m), 1135 (m), 965 (m), 885 (m), 765 (s), 685 (m), 645 (m), $cm^{-1}$; $^1H$ NMR $\delta$ 1.8–2.5 (m, 2 H), 2.6–3.0 (m, 2 H), 3.3–3.8 (m, 2 H), 7.3–7.7 (m, 4 H); exact mass for $C_{11}H_{10}OS_2$ calcd $m/e$ 222.0173, found $m/e$ 222.0179.

**23.** A solution of **22** (25 mg, 0.15 mmol), ethylene glycol (10 $\mu$L), and anhydrous $p$-toluenesulfonic acid (10 mg) in 2 mL of benzene was heated in an apparatus equipped with a Dean–Stark trap for 3.5 h. Conventional workup gave 28 mg of an oil which exhibited four spots by TLC: two unknown components, **23**, and a minor amount of material having the $R_f$ of **21**. Preparative TLC on silica gel (10% E/H eluant gave 6.5 mg (20%) of pure **23**: mp 71–63 °C; IR (KBr) 1765 (vs), 1605 (m), 1570 (m), 1485 (m), 1440 (m), 1360 (m), 1285 (s), 1225 (m), 1125 (m), 1045 (m), 1030 (m), 1015 (s), 950 (m), 830 (m), 805 (m) $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 4.1 (s, 3 H), 4.25 (s, 4 H), 6.9 (d, $J$ = 5.5 Hz, 1 H), 7.15 (d, $J$ = 5.5 Hz, 1 H), 7.5 (t, $J$ = 5.5 Hz, 1 H); exact mass for $M^+ - C_2H_4$ $C_9H_6O_4$ calcd $m/e$ 178.0266, found $m/e$ 178.0272.

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# Diels–Alder Adducts of 1-Benzenesulfonylindole-2-acrylates and 1-(Alkoxycarbonyl)-1,2-dihydropyridines. Intermediates for Synthesis of Iboga Alkaloid Analogues

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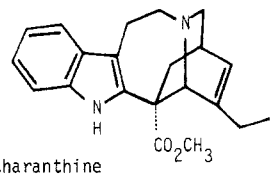
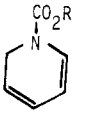
Diels–Alder reactions between methyl 1-benzenesulfonylindole-2-acrylate and several 1-(alkoxycarbonyl)-1,2-dihydropyridines give protected methyl 7-(2-indolyl)-2-azabicyclo[2.2.2]octene-7-carboxylates which serve as intermediates for the synthesis of analogues of the iboga alkaloids. Methods for deprotection of both the carbamate nitrogen and indole nitrogen are reported. The 7-(2-indolyl)-2-azabicyclo[2.2.2]octene-7-carboxylates show a tendency to undergo fragmentation of the C-1,C-7 bond of the 2-azabicyclo[2.2.2]octene ring, probably by retro-Mannich reactions. Several 6-nor-20-deethyl analogues of catharanthine have been prepared from intermediates derived from the deprotected Diels–Alder adducts.

Both biogenetic proposals[1] and retrosynthetic analysis bring the Diels–Alder reaction to the fore in considerations of routes for synthesis of members of the iboga group of indole alkaloids, such as catharanthine. Indeed, the reaction has played a prominent role in synthetic studies in this area.[2-4] We recently demonstrated that esters of 1-benzenesulfonylindole-2-acrylic acid reacted with both 1-(ethoxycarbonyl)- and 1-(methoxycarbonyl)-1,2-dihydropyridine to give Diels–Alder adducts regiospecifically in good yield and with stereoselectivity (~10:1) suitable for elaboration to the iboga skeleton. These adducts proved to be satisfactory intermediates for the synthesis of deethylcatharanthine.[3] In that work the carbamate group derived from the dihydropyridine precursor was removed by vigorous alkaline hydrolysis. With the goal of increasing the synthetic versatility of this type of adduct, we have examined several other 1-substituted dihydropyridines and report here on the Diels–Alder reactions with methyl 1-benzenesulfonylindole-2-acrylate and relevant chemical reactions of the adducts. The (alkoxycarbonyl)-1,2-dihydropyridines which we examined are shown as structures **1a–c** and constitute a series of groups




Catharanthine



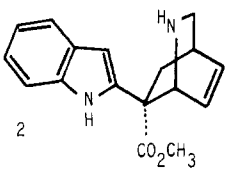

1a R = $C(CH_3)_3$

b R = $CH_2Ph$

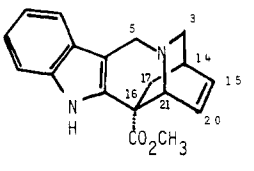
c R = $CH_2CCl_3$

d R = $C_6H_5$

which are subject to nonhydrolytic cleavage. Compound **2** was considered to be a particularly desirable target as an intermediate since it offered the potential reactivity of the indole 3-position and the amine nitrogen as sites for reactions to close the tryptamine bridge of the iboga system or, with one-carbon reagents, the 6-nor skeleton. This structural family has become of interest as the result of encouraging biological results obtained with 6-noranhydrovinblastine.[5]




2

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