1-bromobicyclo[2.2.2]octane, 7697-09-8; 4-acetoxybicyclo[2.2.2]-octane-1-carboxylic acid, 72963-86-1; 4-chlorobicyclo[2.2.2]octane-1-carbonyl fluoride, 94994-06-6; 4-(trifluromethyl)bicyclo-[2.2.2]octan-1-ol, 94994-07-7; 1-(*tert*-butyl)-4-methoxybicyclo-[2.2.2]octane, 81687-94-7; 1-iodo-4-methylbicyclo[2.2.2]octane, 55044-63-8; 1-methoxy-4-methylbicyclo[2.2.2]octane, 6555-95-9; 4-phenylbicyclo[2.2.2]octane-1-amine, 10206-89-0; 4-phenylbicyclo[2.2.2]octane-1-carboxylic acid, 953-69-5; 4-phenylbicyclo[2.2.2]octane-1-carboxamine, 23744-33-4; 1-cyano-4-phenylbicyclo[2.2.2]octane, 950-22-1; 4-[1-(trimethylsilyl)-ethynyl]bicyclo[2.2.2]octane-1-carboxaldehyde, 94994-08-8; 4-iodobicyclo[2.2.2]octane-1-carboxaldehyde, 94994-09-9; 1,1-dichloro-2-(4-iodobicyclo[2.2.2]oct-1-yl)ethene, 94994-10-2; 1-(trimethylsilyl)-2-(4-iodobicyclo[2.2.2]oct-1-yl)ethyne, 94994-11-3; 4-fluorobicyclo[2.2.2]octane-1-carboxylic acid, 78385-84-9; bicyclo[2.2.2]octane-1-methanol, 2574-42-7; 4-nitrobicyclo[2.2.2]octane-1-methanol, 94994-12-4; 4-cyanobicyclo[2.2.2]octane-1-methanol, 94994-13-5; 4-(trifluoromethyl)bicyclo[2.2.2]octane-1-methanol, 94994-14-6; methyl 4-(hydroxymethyl)bicyclo[2.2.2]-octane-1-carboxylate, 94994-15-7; 4-fluorobicyclo[2.2.2]octane-1-methanol, 94994-16-8; 4-chlorobicyclo[2.2.2]octane-1-methanol, 94994-17-9; 4-bromobicyclo[2.2.2]octane-1-methanol, 94994-18-0; 4-methoxybicyclo[2.2.2]octane-1-methanol, 94994-19-1; 4-phenylbicyclo[2.2.2]octane-1-methanol, 23760-80-7; 4-methylbicyclo[2.2.2]octane-1-methanol, 28305-83-1; 4-*tert*-butylbicyclo[2.2.2]octane-1-methanol, 94994-20-4; 4-iodobicyclo-[2.2.2]octane-1-methanol, 94994-21-5; bicyclo[2.2.2]octane-1-carboxaldehyde, 2064-05-3; 4-nitrobicyclo[2.2.2]octane-1-carboxaldehyde, 94994-22-6; 4-cyanobicyclo[2.2.2]octane-1-carboxaldehyde, 94994-23-7; 4-(trifluromethyl)bicyclo[2.2.2]octane-1-carboxaldehyde, 94994-24-8; 4-carbomethoxybicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-25-9; 4-fluorobicyclo-[2.2.2]octane-1-carboxaldehyde, 78385-82-7; 4-chlorobicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-26-0; 4-bromobicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-27-1; 4-methoxybicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-28-2; 4-phenylbicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-29-3; 4-methylbicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-30-6; 4-*tert*-butylbicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-31-7; 4-ethynylbicyclo-[2.2.2]octane-1-carboxaldehyde, 94994-32-8; 4-ethynylbicyclo-[2.2.2]octane-1-methanol, 94994-33-9; 4-ethynylbicyclo[2.2.2]octane-1-carboxylic acid, 94994-34-0; bicyclo[2.2.2]octane-1-carboxylic acid, 699-55-8; 4-bromobicyclo[2.2.2]octane-1-carboxylic acid, 1989-50-0; 4-chlorobicyclo[2.2.2]octane-1-carboxylic acid, 1007-73-4; 4-methylbicyclo[2.2.2]octane-1-carboxylic acid, 702-67-0; 4-nitrobicyclo[2.2.2]octane-1-carboxylic acid, 775-65-5; 4-cyanobicyclo[2.2.2]octane-1-carboxylic acid, 15941-09-0; 1-methoxybicyclo[2.2.2]octane, 7697-14-5; 4-methoxybicyclo[2.2.2]octane-1-carboxylic acid, 773-34-2; methanol, 67-56-1; iodine monochloride, 7790-99-0; chlorine, 7782-50-5; iodine, 7553-56-2; iodotrimethylsilane, 16029-98-4; 1-nitro-4-phenylbicyclo[2.2.2]octane, 64852-68-2; methyl 4-phenylbicyclo[2.2.2]octane-1-carboxylate, 23062-52-4; chlorotrimethylsilane, 75-77-4; *N*-formylpiperidine, 2591-86-8; carbon monoxide, 630-08-0.

Stereoselective Synthesis of an Analogue of Podophyllotoxin by an Intramolecular Diels–Alder Reaction

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The dihydrobenzocyclobutene **90** having a 4-hydroxycrotonate unit attached via an ester linkage as an internal dienophile can be cyclized to a 3:1 mixture of the trans lactone **92** (an analogue of podophyllotoxin, **1**) and the cis lactone **93**. This stereoselective reaction proceeds via the intermediacy of the *o*-quinodimethane **91** which cyclizes from the endo transition state **91n** in preference to the exo-one **91x**, presumably because of stabilization of the former by secondary orbital overlap. This result provides evidence that a proposed general route to the synthesis of podophyllotoxin, **1**, and its analogues via the internal cycloaddition of the *o*-quinodimethane **8** to **9n** may prove successful. Several possible approaches to the synthesis of the *trans*-2-aryldihydrobenzocyclobutenol **4** are described. The benzyne **11** was prepared and underwent [2 + 4] but no [2 + 2] cycloadditions. Although the 2-bromobenzocyclobutenone **23** could be synthesized in an efficient manner, it proved impossible to convert it into **4** by means of the aryl organometallic reagents **22ab**. The bromo epoxide **52** was prepared and subjected to metal–halogen exchange and Lewis acid catalyzed epoxide rearrangement in an attempt to prepare **4**. The aldehyde **56** was obtained in this reaction, clearly indicating that the desired intermediate **54** had been formed but could not be trapped under these conditions. Two ring contraction routes to **4** are also described, both beginning with the 1-indanone **74** prepared in good yield from piperonal **14**. The diol monomesylate **78**, prepared from **74**, suffered base-catalyzed E2 elimination rather than the desired rearrangement to **80**. The diazo ketone **83** underwent Wolff rearrangement to give the desired ester **84**, but only in 7% yield. Two interesting transformations were observed in these ring contraction schemes, namely the formation of the oxathiole dioxide **77** on mesylation of the ketol **75** and the preparation of the diazirene **86** on photolysis of the diazo ketone **83** at long wavelengths. The ester **84** was then saponified to the acid **87** which was coupled with methyl 4-hydroxycrotonate, **5**, to give **90**. The assignment of the structures of the products of thermolysis of **90** was based on high field ^{1}H NMR and analogy to the spectra of similar compounds in the literature.

Introduction

In the early 1970's several derivatives of podophyllotoxin **1**, the active principle isolated from podophyllin,[2] began to show great promise as cancer chemotherapeutic agents.[3] The results of extensive phase I clinical testing produced two drugs, designated VM-26 (for 4′-demethyl-1-*O*-[4,6-*O*-(2-thienylmethylene)-β-D-glucopyroanosyl]epipodophyllotoxin, NSC-122819) (**2**) and VP-16-213 (for 4′-demethyl-1-*O*-[4,6-*O*-(ethylidene)-β-D-glucopyranosyl]epipodophyllotoxin, NSC 141540) (**3**), which showed acceptable toxicity levels[4] and showed useful therapeutic

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983; Fellow of the Alfred P. Sloan Foundation, 1979–1981.

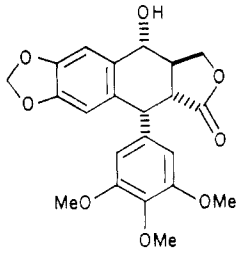
(2) Hartwell, J.; Shear, M. *Cancer Res.* **1947**, *7*, 716.

(3) (a) Vaitkevicius, R. K.; Reed, M. L. *Cancer Chemother. Rep.* **1966**, *50*, 565. (b) For a recent review of podophyllotoxin **1**, see: Jardin, I. *Med. Chem. (Wiley)* **1980**, *16*, 319.

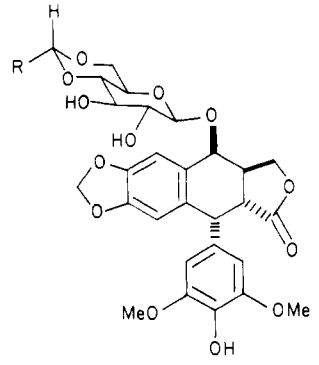
(4) Muggia, F. M.; Selawry, O. S.; Hansen, F. H. H. *Cancer Chemother. Rep.* **1971**, *55*, 575.

0022-3263/85/1950-1087$01.50/0

benefit against Hodgkin's disease.[5] Further testing has shown these compounds to be effective in cancer chemotherapy either alone[6] or in combination with other antineoplastic agents.[7]



1



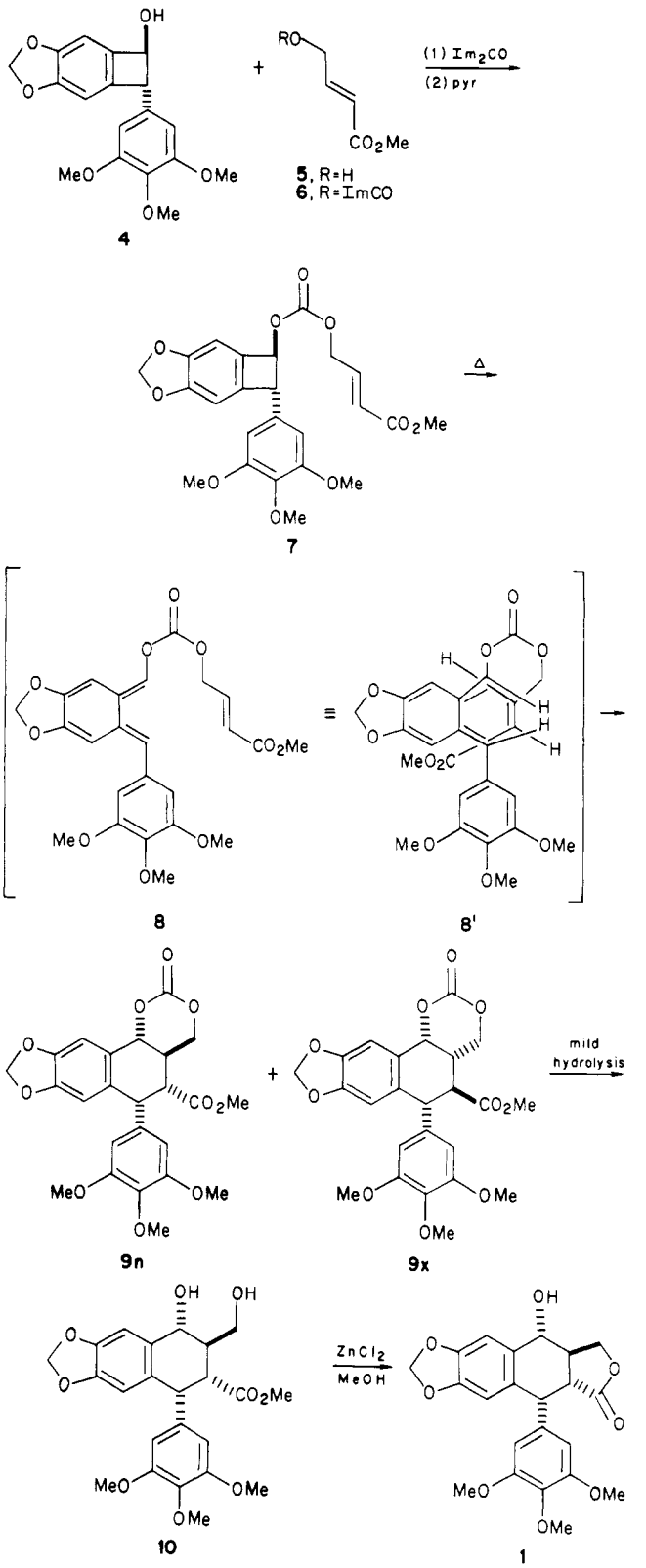
2, R = 2-thienyl VM-26
3, R = Me VP-16-213

The active drugs **2** and **3** were prepared by Kuhn and von Wartburg from podophyllotoxin **1** via several steps in relatively good overall yield.[8] Three syntheses of podophyllotoxin **1** have been reported. The original synthesis of Gensler and Gatsonis[9] produced a mixture of **1** and its C2-epimer picropodophyllin in the final step in which the desired isomer was the minor isomer. Recently Rodrigo[10] and Kende[11] have reported very successful and elegant approaches which produced **1** in 12 steps from bromopiperonal in 9% and 4.5% overall yields, respectively. We now wish to report the results of our research aimed at producing **1** and its analogues by a different cycloaddition route.

Results and Discussion

Our proposed route to **1**, and thence to the drugs **2** and **3**, involved as the key step an intramolecular cycloaddition of a disubstituted *o*-quinodimethane such as the carbonate **8**. This compound would be prepared from the *trans*-2-aryldihydrobenzocyclobutenol **4** and the known alcohol **5**.[12] Conversion of **5** into the imidazole carbonate **6** followed by reaction with **4** should give the mixed carbonate **7**. Thermolysis of **7** at fairly low temperatures (~100–150 °C)[13] should produce specifically the trans,trans-disubstituted carbonate **8** which should undergo intramolecular cycloaddition to the ester to give the tetralin products **9n** and/or **9x**. If the Alder endo transition state rules hold for this cycloaddition,[14] namely if the endo transition state

Scheme I



(5) Dombernowsky, P.; Nissen, N. I.; Larsen, V. *Cancer Chemother. Rep.* **1972**, *56*, 71; *Eur. J. Cancer* **1976**, *12*, 181.

(6) (a) Loike, J. D. et al. *Cancer Res.* **1978**, *38*, 2688. (b) Tucker, R. D. et al. *Cancer* **1978**, *41*, 1710. (c) Brunner, K. W. "Abstracts of Papers"; Chemotheraphy Foundation Symposium III, 1978, p 38. (d) Eagen, R. T. *Ibid.* **1978**, 41. (e) Radice, P. A.; Bunn, P. A.; Ihde, D. C. *Cancer Treat. Rep.* **1979**, *63*, 1231.

(7) Yalowich, J. D.; Fry, D. W.; Goldman, T. D. *Cancer Res.* **1982**, *42*, 3648.

(8) (a) Kuhn, M.; von Wartburg, A. *Experentia* **1963**, *19*, 391. (b) Kuhn, M.; Keller-Juslen, C.; von Wartburg, A. *Helv. Chim. Acta* **1969**, *52*, 944. (c) Kuhn, M.; von Wartburg, A. *Ibid.* **1969**, *52*, 948. (d) Keller-Juslen, C.; von Wartburg, A.; Stahelin, H. *J. Med. Chem.* **1971**, *14*, 936.

(9) Gensler, W. J.; Gatsonis, C. D. *J. Am. Chem. Soc.* **1962**, *84*, 1748; *J. Org. Chem.* **1966**, *31*, 4004.

(10) (a) Rajapaksa, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208. (b) Rodrigo, R. *J. Org. Chem.* **1980**, *45*, 4538. (c) Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 354.

(11) (a) Kende, A. S.; King, M. L.; Curran, D. P. *J. Org. Chem.* **1981**, *46*, 2826. (b) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082. (c) For similar work, see: Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Chem. Commun.* **1980**, 262.

(12) (a) Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866. (b) Ducher, S.; Journou, M. N. *Ann. Chim. (Paris)* **1973**, [14] *8*, 359. (c) Rambaud, R. *Bull. Soc. Chim. Fr.* **1934**, [5] *1*, 1317; *Ibid.* **1969**, 1340.

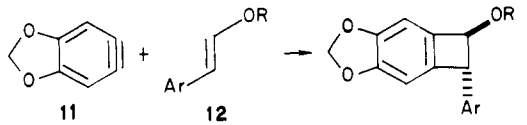
(13) For a good review of the use of *o*-quinodimethanes in Diels–Alder reaction, see: (a) Oppolzer, W. *Synthesis* **1978**, 793. (b) Kametani, T. *Pure and Appl. Chem.* **1980**, *51*, 747. (c) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (c) Oppolzer, W. *Heterocycles* **1980** *14*, 1615. (e) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3.

(14) The results in the literature, especially those from Oppolzer's group,[13a] are somewhat contradictory regarding the preferred transition-state geometry. However, these cases have generally not involved a dienophile substituted with an electron-withdrawing group, and thus one might expect a stronger endo preference in the case of **8**.

8′ is more stable than the exo-one, then one would expect the endo product **9n** to predominate over the *exo*-**9x**. Mild hydrolysis of **9n** would give the known compound methyl podophyllate **10**, which has been converted into podophyllotoxin **1** by Kuhn and von Wartburg[8a] by treatment with zinc chloride in methanol. This route offered the potential of being a very efficient, convergent approach to **1** which might also be of value for analogue preparation.

The synthetic challenge of this research program is an efficient preparation of the unknown *trans*-2-aryldihydrobenzocyclobutenol **4**. Although many synthetic approaches have been attempted, we have yet to prepare this compound. However, we have synthesized its analogue **87** (vide infra) and have successfully carried out a similar key cycloaddition step to give stereoselectively the lactone **92**, an analogue of **1**. We now describe our synthetic attempts to prepare **4** and our successful preparation of lactone **92**.

Benzyne Approach. There are many methods known for the preparation of dihydrobenzocyclobutenes.[15] One of the most direct approaches to the desired dihydrobenzocyclobutenol would be the [2 + 2] cycloaddition of benzyne to a β-substituted styrene. This route is based on the work of Wasserman[16] who showed that the reaction of benzyne (generated by diazotization of anthranilic acid) with cis or trans ethyl propenyl ethers gave fair yields of the expected dihydrobenzocyclobutenes with good stereoselectivity. Therefore we felt it was likely that 4,5-(methylenedioxy)benzyne **11** might react with a 2′-alkoxy-3,4,5-trimethoxystyrene **12** to produce the desired cycloadduct **13**. The benzyne **11** had not been reported

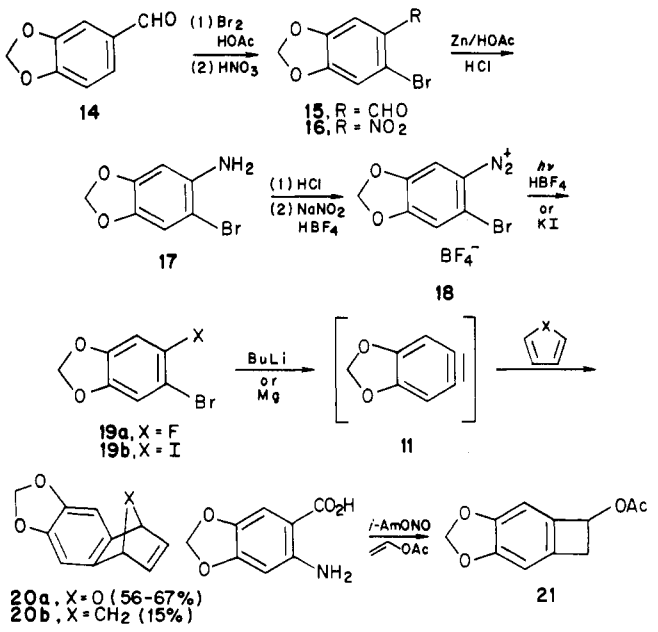


11 12 13

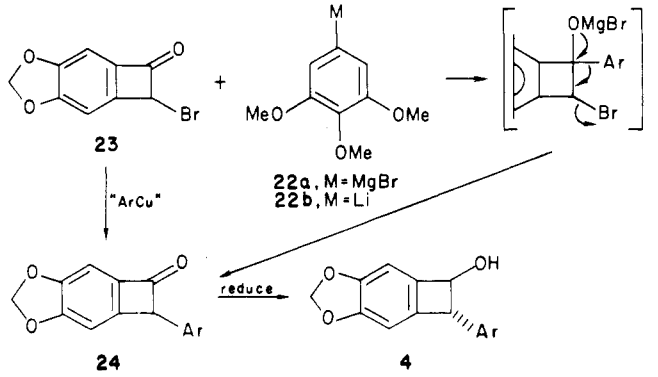
Ar = 3,4,5-$(OMe)_3C_6H_2$

previously in the literature but could be prepared in relatively straightforward fashion from piperonal **14**. The known[17] 2-bromo-4,5-(methylenedioxy)nitrobenzene **16** was prepared in two steps from piperonal **14** via bromopiperonal **15**. Reduction of **16** with zinc in acetic acid and concentrated HCl gave a 96% yield of the amine **17**. Diazotization of the hydrochloride salt of **17** with sodium nitrite and fluoroboric acid produced the diazonium tetrafluoroborate **18** in good yield. One potential precursor of the desired benzyne was the fluoride **19a**, but it could be prepared only in poor (13%) yield. The iodide **19b** was readily prepared from **18** by treatment with KI in 93% overall yield from **17**. The desired benzyne **11** could indeed be prepared from **19b** by either of two routes. Treatment of **19b** with *n*-butyllithium in a 1:1 mixture of THF and furan as solvent at −78 °C afforded a 67% yield of the expected [4 + 2] cycloaddition product **20a**. This compound could also be prepared in 88% yield by treatment of **19b** with magnesium in THF:furan at 65 °C. Use of cyclopentadiene in place of furan in this second approach afforded the methylene analogue **20b** in only 15% yield. These results indicated that benzyne **11** was indeed formed and underwent typical [4 + 2] cycloadditions. However, we were completely unable to effect any [2 + 2] cycloadditions of **11** with a variety of olefins, including *cis*-β-ethoxystyrene, *trans*-β-pyrrolidinostyrene,[18] allene, ethyl vinyl ether, methyl acrylate, etc.

Scheme II



Scheme III



Since the successful [2 + 2] cycloadditions of Wasserman and Kuehne had used benzyne generated by diazotization of anthranilic acid, we decided to examine this route to the benzyne **11**. Diazotization of this known amino acid, 4,5-(methylenedioxy)-2-aminobenzoic acid,[19] with isoamyl nitrite in the presence of several potential trapping agents—ethyl vinyl ether, vinyl acetate, methyl acrylate—gave only poor yields of the desired [2 + 2] adducts. For example the benzocyclobutene **21** was produced in an isolated yield of 8% by treating the substituted anthranilic acid with isoamyl nitrite in refluxing vinyl acetate as solvent. Thus to date all attempts to utilize the benzyne **11** in a [2 + 2] cycloaddition approach to molecules related to **4** have failed.

2-Bromobenzocyclobuten-1(2*H*)-one Approach. A second approach to molecules such as **4** involved the addition of the trimethoxyphenyl organometallic reagent **22** to 2-bromobenzocyclobuten-1(2*H*)-one (**23**) to give the halohydrin which could be rearranged thermally to the 2-arylbenzocyclobuten-1(2*H*)-one (**24**). Rearrangement of

(15) (a) Klundt, I. L. *Chem. Rev.* **1970**, *70*, 471. (b) Thummel, R. P. *Acc. Chem. Res.* **1980**, *13*, 70.

(16) (a) Wasserman, H. H.; Solodar, J. *J. Am. Chem. Soc.* **1965**, *87*, 4002. (b) Wasserman, H. H.; Solodar, A. J.; Keller, L. S. *Tetrahedron Lett.* **1969**, 5597.

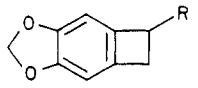
(17) Craig, P. N.; Gordon, M.; Lafferty, J. J.; Lester, B. M.; Gaggiomo, A. J.; Zirkle, C. L. *J. Org. Chem.* **1961**, *28*, 1138.

(18) Kuehne has reported that enamines react well with benzyne itself to give the [2 + 2] cycloadduct. Kuehne, M. E. et al. *J. Am. Chem. Soc.* **1962**, *84*, 837; *Tetrahedron Lett.* **1969**, 4163.

(19) Mitscher, L.; Gracey, H. E.; Clark, G. W., III; Suzuki, T. *J. Med. Chem.* **1978**, *21*, 485.

halohydrins of this sort are well-known and have been carried out on the halohydrins themselves or on their salts.[20] Compound **24** might also be available from the reaction of **23** or its derivatives with an aryl organocuprate. Reduction of **24** to the *trans*-alcohol would then give the desired alcohol **4**.

There are several potential routes from piperonal to the bromo ketone **23**, of which two seemed the most convenient, namely CrO_3 oxidation of the 1-bromodihydrobenzocyclobutene[21] or bromination of the benzocyclobutenone.[22] Although we were able to prepare 1-bromo-4',5'-(methylenedioxy)dihydrobenzocyclobutene (**25b**) by NBS bromination of the corresponding hydrocarbon **25a**, the multistep nature of the preparation of **25a**[23] prevented us from carrying out this reaction on a large scale. For this reason, we decided to prepare the necessary benzocyclobutenone **31** by an application of the Kametani procedure.[24]

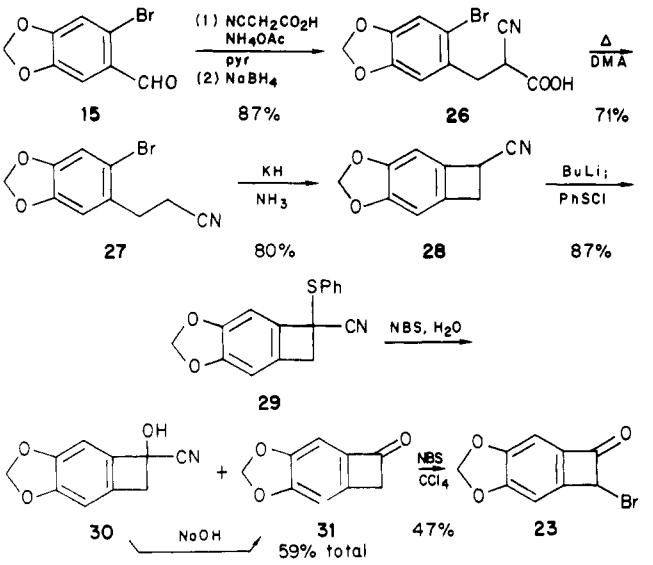


25a, R = H
25b, R = Br

Treatment of bromopiperonal **15** with cyanoacetic acid in pyridine afforded the Knoevenagel product which was reduced with borohydride to give the cyanocinnamic acid **26** in 87% overall yield. Decarboxylation of the acid in hot dimethylacetamide (170 °C) furnished a 71% yield of the nitrile **27**. Reductive cyclization of **27** to give **28** was quite variable when potassium amide prepared from potassium and ammonia was used, with yields varying from 10% to 50%. However, the use of potassium hydride afforded much more consistent and better results, producing **28** in 80% yield. The excellent procedure of Watt[25] was used to convert **28** into **31**, namely thiophenylation to give in 87% yield the sulfide **29** which was oxidized with aqueous NBS to give 20% of the desired ketone **31** and a large amount of a more polar product which proved to be the cyanohydrin **30**. Treatment of **30** with strong base afforded an additional 39% of the ketone **31** bringing its overall yield from **29** to nearly 60%. Final bromination of **31** was effected with NBS to produce the bromo ketone **23**.

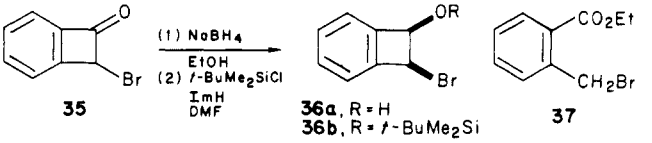
The required 3,4,5-trimethoxyphenyl bromide (**32**) was known[26] and could be prepared from 3,4,5-tribromo-2,6-dimethoxyphenol (**33**) by reduction and methylation[26b,27] or from 2,6-dimethoxyphenol (**34**) by selective bromination and methylation.[26d] Preparation of the Grignard reagent **22a** or the organolithium **22b** from **32** was effected by

Scheme IV



normal routes. However, all attempts to add the Grignard reagent **22a** or the organolithium **22b** to the bromobenzocyclobutenone **23** to give the ketone **24** were completely unsuccessful. In no case were alcoholic or rearranged ketonic products obtained, the main product isolated being the protonated organometallic, 1,2,3-trimethoxybenzene. Thus this route was abandoned.

We did investigate in a model system the reduction of a substituted benzocyclobutenone related to **24** to find conditions under which the alcoholate was stable to ring opening. The known 2-bromobenzocyclobutenone **35**, prepared by the route of Cava,[22] was reduced with sodium borohydride in ethanol at 25 °C to give an 81% yield of a single isomer of the alcohol **36a**. We have assigned the



cis stereochemistry to this compound based on the assumption that hydride would attack trans to the bromide atom. The alcohol could be protected as its *tert*-butyldimethylsilyl (TBS) ether **36b** in 84% yield under the normal conditions. It is somewhat curious that the alcoholate produced in the reduction does not open up the strained benzocyclobutene ring, since treatment of **35** with potassium carbonate in ethanol at 25 °C overnight produces the benzoate **37**. We will describe in the next section an alcoholate similar to **36a** which does indeed open the benzocyclobutene ring.

Organometallic–Epoxide Route. A third potential route to **4** involved the treatment of a stilbene oxide bearing a bromide at the ortho position of **38** with *n*-butyllithium and magnesium bromide to effect a rearrangement to the diphenyl acetaldehyde **39** which would then be attacked intramolecularly by the organometallic center to give the magnesium alcoholate **40** which would be protonated to give **4** and its cis isomer. This process has been used recently by Durst to produce some substituted cyclobutenols.[28] The trans stereochemistry of the alco-

(20) (a) Huang, R. L. *J. Org. Chem.* **1954**, *19*, 1363; *J. Chem. Soc.* **1957**, 4089. (b) Hussey, A. S.; Herr, R. R. *J. Org. Chem.* **1959**, *24*, 843 and references therein.

(21) This reaction has been successfully effected in the 4,5-unsubstituted system. (a) Cava, M. P.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2255. (b) Horner, L.; Subramanian, P. V. *Tetrahedron Lett.* **1965**, 101.

(22) This bromination has been carried out on the parent system. Cava, M. P.; Mangold, D.; Muth, K. *J. Org. Chem.* **1964**, *29*, 2947.

(23) Spangler, R. J.; Beckmann, B. G. *Tetrahedron Lett.* **1976**, 2517.

(24) Kametani, T. et al. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1712; *Tetrahedron* **1973**, *29*, 73.

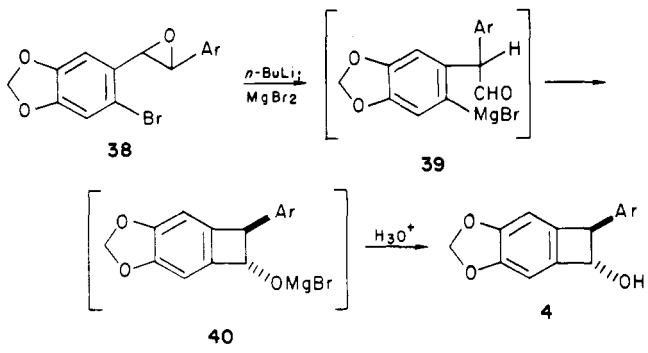
(25) Selikson, S. J.; Watt, D. S. *Tetrahedron Lett.* **1974**, 3029.

(26) (a) Kohn, M.; Steiner, L. *J. Org. Chem.* **1947**, *12*, 30. (b) Hardy, G.; Sword, I. P.; Hathway, D. E. *J. Labelled Compd.* **1972**, *8*, 221. (c) Kozak, I.; Kronrad, L.; Prochazka, M. *Ibid.* **1978**, *15*, 401. (d) Foley, J. W. *U. S. Patent* 4 182 912, 1979; *Chem. Abstr.* **1980**, *92*, P:163705x. (e) Friedman, D.; Ginsburg, D. *J. Org. Chem.* **1958**, *23*, 16.

(27) Although the yield of the zinc reduction and methylation could be greatly increased (from 7% to 23%) by using preparative HPLC to separate the mixture of isomers, the method of Foley[26d] is significantly better (50% overall yield).

(28) While our work on these rearrangements was underway, Durst published his preliminary results on the same process: (a) Dhawan, K. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* **1980**, *45*, 922. The full paper has also appeared: (b) Akgun, E.; Glinski, M. B.; Dhawan, K. L.; Durst, T. *J. Org. Chem.* **1981**, *46*, 2730.

Scheme V



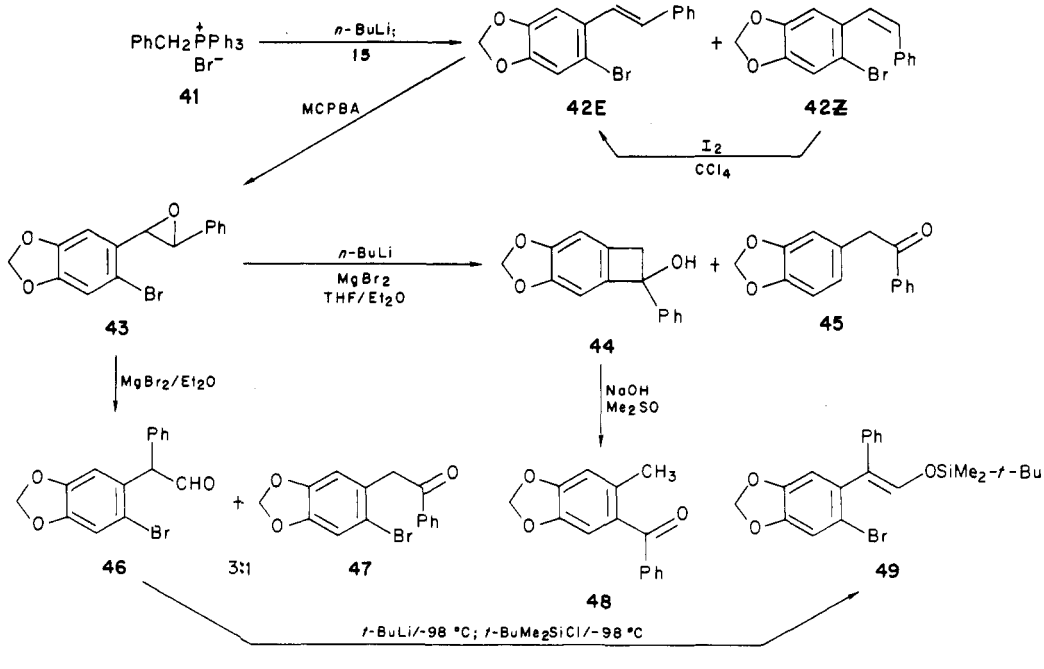
holate **40** is expected due to steric reasons (preferred conformation of the aldehyde of **39** having the carbonyl oxygen anti to the aryl group) and literature precedent.[28b] This approach seemed to represent a very economical and convergent approach to **4**.

Before preparing the trimethoxyphenyl system, we carried out model studies of the simpler phenyl analogue **43**. Preparation of **43** was carried out as follows. Reaction of the salt **41** with *n*-butyllithium gave the phosphorane which was condensed with bromopiperonal **15** to give a mixture of the (*E*)- and (*Z*)-stilbenes **42EZ**. Although these compounds could be purified by preparative HPLC, it was simpler to isomerize **42Z** to **42E** with iodine and then isolate only **42E**. Epoxidation of **42E** gave the desired epoxide **43**. Treatment of a solution of **43** in THF at −78 °C with an ethereal solution of magnesium bromide followed by the addition of *n*-butyllithium, warming to room temperature, and normal workup gave none of the desired dihydrobenzocyclobutenol. Rather there was obtained a 33% yield of the tertiary alcohol **44** along with 5% of the ketone **45** and 28% recovered starting material. This result would imply that the *o*-lithio or -magnesio epoxide corresponding to **43** rearranged at least substantially to the *o*-metallo arylmethyl phenyl ketone corresponding to **45** which then accounts for the formation of the observed products. We determined independently that the magnesium bromide etherate does not cause any rearrangement at −78 °C but only upon warming to −35 °C or so and thus it is likely that halogen–lithium exchange occurs first. In order to determine if the aldehyde could be forming at all in this rearrangement of the metallo epoxide, we treated the bromo epoxide **43** with ethereal magnesium bromide and obtained an 80% yield of an approximately 3:1 mixture of the aldehyde **46** and the ketone **47**. Therefore it is somewhat perplexing that no product arising from the metallo aldehyde corresponding to **46** was obtained in this reaction. It is possible that the desired 2-phenylbenzocyclobutenol anion was formed and was unstable under the reaction conditions, rearranging to the *o*-[(arylcarbonyl)phenyl]methyl anion, a process we have observed in other cases (vide infra). For example, treatment of **44** with sodium hydroxide in Me_2SO-d_6 for 30 min gave exclusively the ketone **48**.

One final attempt to effect the desired cyclization in the model system was made, namely treatment of **46** with 1 equiv of *tert*-butyllithium at −98 °C, to try to effect lithium–halogen exchange and cyclization, followed by the addition of *tert*-butyldimethylsilyl chloride at −98 °C and warming to room temperature. In this way we hoped to trap the alcoholate at low temperature before it rearranged. The only product isolated after preparative TLC was the silyl enol ether **49**. No evidence for the presence of benzocyclobutenols was obtained.

To avoid the problems associated with mixtures of rearranged products (phenyl vs. H migration) from the stilbene oxides (e.g., **43**), we decided to use the corresponding 1,1-diarylethylene oxide which could rearrange only to the desired aldehyde via H migration. We prepared the correct epoxide **52** in the trimethoxyphenyl system as follows. The bromide **32** was treated with *n*-butyllithium at −78 °C and bromopiperonal **15** was added to give a complex mixture from which the benzhydrol **50** could be isolated by preparative HPLC in 37% recrystallized yield. This was then oxidized to the benzophenone **51** in quantitative yield by Jones oxidation. Carrying out the two steps without an intermediate purification gave **51** in 41% overall yield based on **32**. Epoxidation via the Corey method[29] using dimethylsulfonium methylide gave a 97%

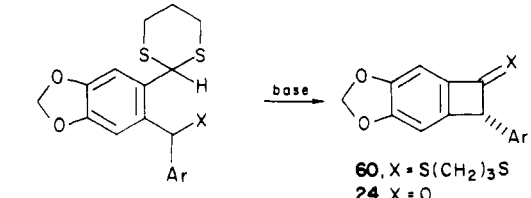
Scheme VI



yield of the desired epoxide **52**. We first checked the rearrangement of the bromo epoxide **52** with ethereal magnesium bromide which proceeded as expected to give the bromoaldehyde **53** in 97% crude yield. However, rearrangement–cyclization of the anion of **52** was again unsuccessful but for a different reason. Treatment of a mixture of **52** and 1.1 equiv of *tert*-butyldimethylsilyl chloride (TBSCl) in ether at −78 °C with ethereal magnesium bromide and then a pentane solution of *tert*-butyllithium followed by normal workup gave a mixture of products. Purification by preparative TLC gave as the major isolated product the aldehyde **56** in 18% yield. The formation of this product implies clearly that the desired rearrangement and cyclization are indeed occurring but that the intermediate alcoholate **54** is unstable under the reaction conditions and opens the cyclobutane ring to give the *o*-formylbenzhydryl anion **55** which is finally protonated to give the observed product **56**. The magnesium alkoxide **54** is presumably too unreactive to be silylated by the TBSCl which was added for that exact purpose. Several other variations of this reaction were also tried without success. Thus unless a better trapping agent can be found which would survive the anion formation and rearrangement conditions, this direct approach remains unworkable.

Several additional attempts were made with intermediates in this route. For example, treatment of **53** with trimethylsilyl iodide to give the corresponding iodohydrin trimethylsilyl ether[30] followed by treatment with *tert*-butyllithium did not give the desired dihydrobenzocyclobutenol silyl ether. Treatment of the dimethyl acetal **57**, prepared in quantitative yield from **53**, with magnesium bromide and *tert*-butyllithium gave a 53% yield of a 2:1 isomeric mixture of methyl enol ethers **58**, with no benzocyclobutene products observed.

Other Cyclization Routes. We also attempted to assemble the benzocyclobutene system by preparing an ortho-disubstituted piperonyl derivative with substituents which would permit the final closing of the cyclobutane ring by an alkylation process. Namely we wanted to construct the benzhydryl halide **59** with a dithiane unit in the required ortho position to allow for internal alkylation (perhaps via the dithio *o*-quinodimethane) to give **60** which could be converted into **4** by way of **24**. The

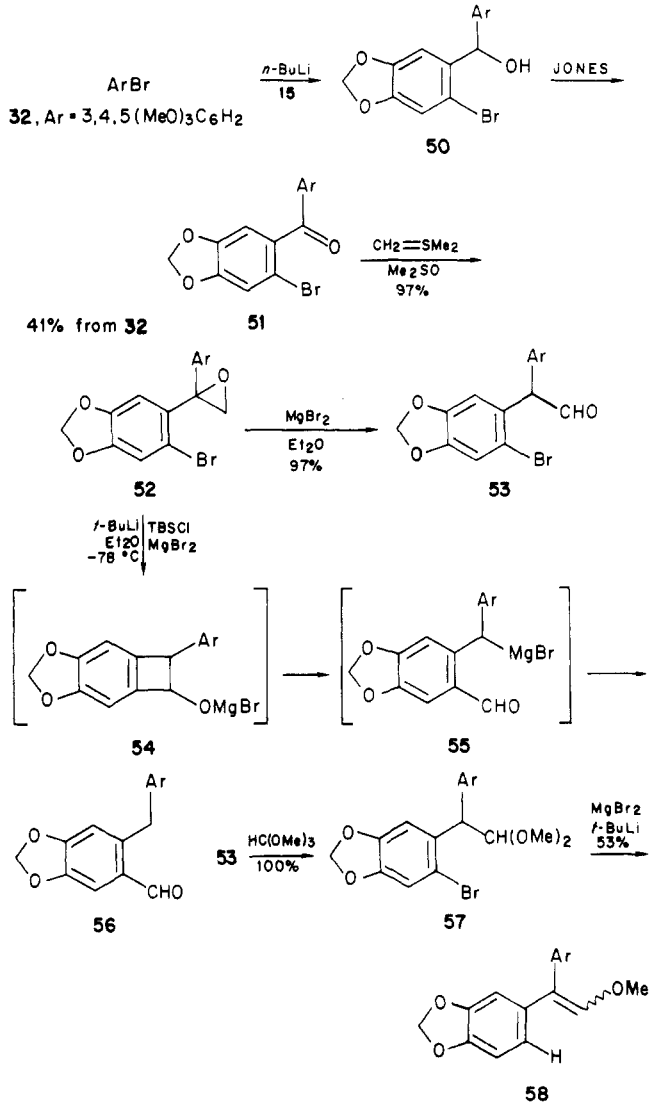


59, Ar = 3,4,5-$(OMe)_3C_6H_2$

60, X = $S(CH_2)_3S$
24, X = O
4, X = β-OH, α-H

most direct route to **59** involved condensation of the dianion of the dithiane from bromopiperonal **15** at the aryl carbon followed by conversion of alcohol to halide. Therefore bromopiperonal **15** was converted into its dithiane **61** in 90% yield by the usual method. Treatment of **61** with 2 equiv of *tert*-butyllithium followed by deuteration (D_2O) gave the expected dideuterated product **62a** in 74% yield with a small contamination by the monodeuterio product **62b**, in which the deuterium was located nearly exclusively at the dithiane carbon. This would imply that lithium–halogen exchange occurs initially to

Scheme VII

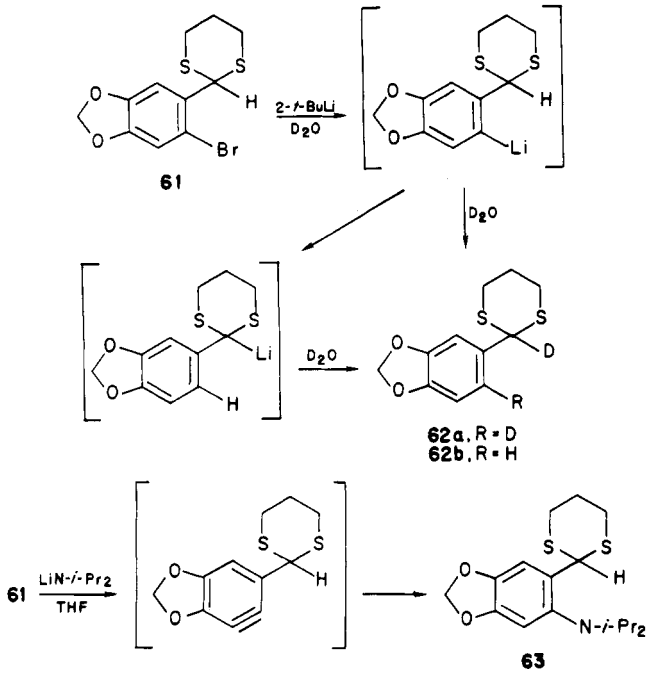


give the aryllithium which then undergoes two competing deprotonations, one by *tert*-butyllithium to give the dianion and the second by the aryllithium itself which deprotonates the dithiane to place a hydrogen atom in the place of the original bromine. Addition of D_2O would then give the observed products **62ab**. One should be able to avoid the somewhat annoying problem of partial loss of the aryl anion by first preparing the anion of the dithiane with a strong base other than an alkyllithium and then adding the alkyllithium in a second step to effect lithium–halogen exchange and produce the dianion. Therefore, the bromo dithiane **61** was treated with 1.1 equiv of lithium diisopropylamide at −78 °C for 2 h and then 25 °C for 3 h followed by quenching with D_2O. However, the expected monodeuterio bromo dithiane was not formed. Instead a complex mixture of products was produced, from which could be isolated a compound having spectral properties consistent with the 6-diisopropylamino dithiane **63**. This compound is presumably formed via the intermediacy of the benzyne prepared by elimination of HBr from **61** with the strong base.

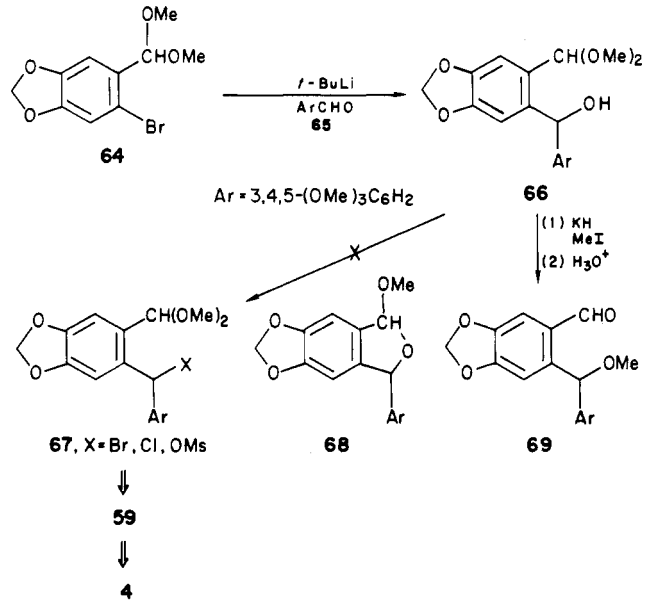
A second similar approach began with the dimethyl acetal **64** prepared in quantitative yield from bromopiperonal **15**. Lithiation and condensation with 3,4,5-trimethoxybenzaldehyde (**65**) gave the known[10b,c] alcohol **66** in 77% yield. All attempts to convert the alcohol into a leaving group such as bromide, chloride, or mesylate to give

(29) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(30) Jung, M. E.; Mossman, A. B.; Lyster, M. A. *J. Org. Chem.* **1978**, *43*, 3698.

Scheme VIII



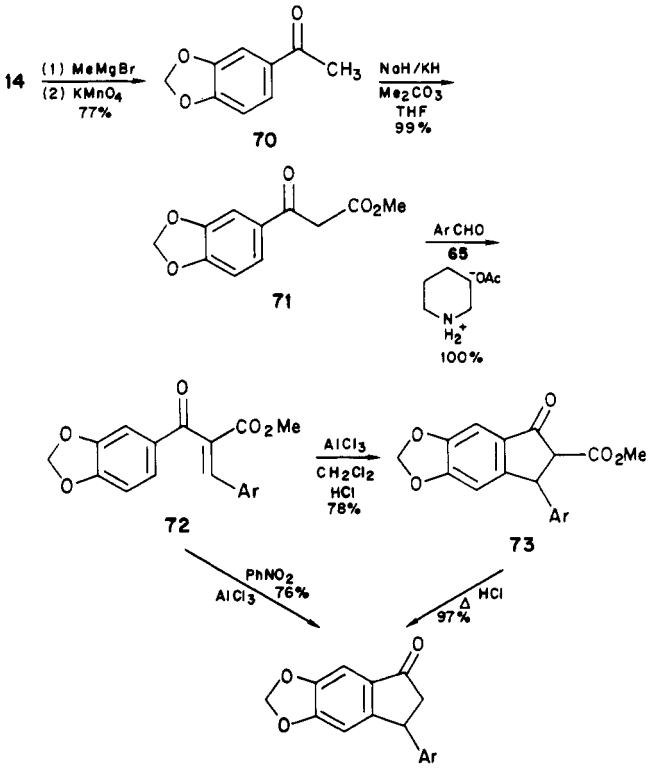
Scheme IX



compound **67** were unsuccessful producing instead either the cyclic acetal **68** or the methoxy aldehyde **69**. The latter compound is presumably formed via internally assisted (by one of the methoxyl groups) solvolysis of the benzhydryl leaving group followed by eventual hydrolysis of the cationic species at the aldehyde carbon. An authentic sample of the methoxyaldehyde **69** was prepared by methylation of the alcohol of **66** followed by acidic hydrolysis. Thus our inability to prepare **67** prevented us from producing **59** by this route and attempting the alkylative cyclization.

Ring Contraction Routes. Our final attempts to prepare **4** were based on the possibility of constructing a substituted indan system and subjecting it to one of several methods for ring contraction in order to produce a benzocyclobutene which could then be converted to **4**. Of the several possible methods for ring contraction, two looked feasible for preparing the very strained benzocyclobutene system: (1) an anionic glycol monosulfonate rearrangement, which has been used to prepare strained systems

Scheme X



such as cyclobutanones[31a] and even trans-fused bicyclo[4.1.0]heptan-2-one;[31b] (2) a Wolff rearrangement of a 2-diazo-1-indanone, a reaction precedented in this system.[32] Thus we investigated the construction of 3-aryl indanones such as **74**.

(a) Glycol Monosulfonate Rearrangement. Piperonal **14** was converted into the known[33] methyl ketone **70** in two steps in 77% yield. Carbomethoxylation of **70** afforded the β-keto ester **71** which was reacted with the aldehyde **65** in a Knoevenagel condensation to produce the enone **72** in quantitative crude yield from **70**. Nazarov-type cyclization of **72** by a modification of the method of Vecchionacci[34] with aluminum chloride in dichloromethane furnished in 78% yield the indanone ester **73**, which could be decarbomethoxylated to give the desired indanone **74** in 97% yield. By the use of nitrobenzene as solvent, both operations could be carried out in one step thereby converting **72** into **74** in 76% yield. Thus the indanone **74** is available from piperonal via five simple steps in 58% yield.

With the indanone **74** in hand in large quantities, we investigated the conversion of it into the necessary glycol monosulfonate **78**. Preparation of the 2-hydroxyindanone **75** from **74** was accomplished by either of two routes, namely direct hydroxylation of the enolate ion with the MoOPH reagent[35] or peracid oxidation of the trimethylsilyl enol ether.[36] We assigned the structure as trans for two

(31) (a) Ghera, E. *J. Org. Chem.* **1968**, *33*, 1042. (b) Paukstelis, J. V.; Kao, J. *J. Am. Chem. Soc.* **1972**, *94*, 4783.

(32) Blomquist, A. T.; Bottomley, C. G. *Liebigs Ann. Chem.* **1962**, *653*, 67.

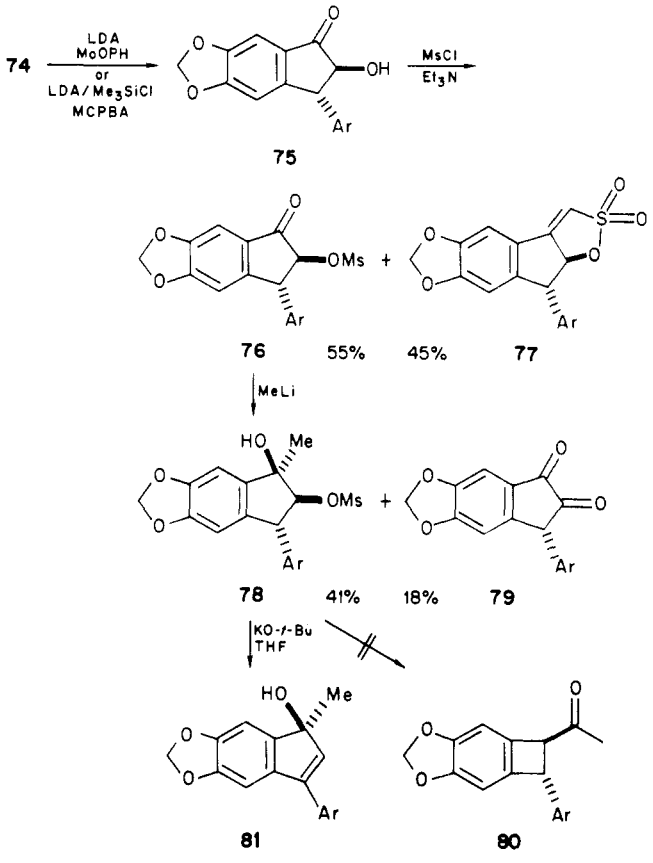
(33) (a) Guziec, F. S., Jr.; Luzzio, F. A. *Synthesis* **1980**, 691. (b) Richardson, T.; Robinson, R.; Seijo, E. *J. Chem. Soc.* **1937**, 835.

(34) Vecchionacci, J.-P.; Canevet, J.-C.; Graff, Y. *Bull. Soc. Chim. Fr.*, **1974**, 1683.

(35) Vedejs, E.; Engler, D. A.; Telschew, T. E. *J. Org. Chem.* **1978**, *43*, 188.

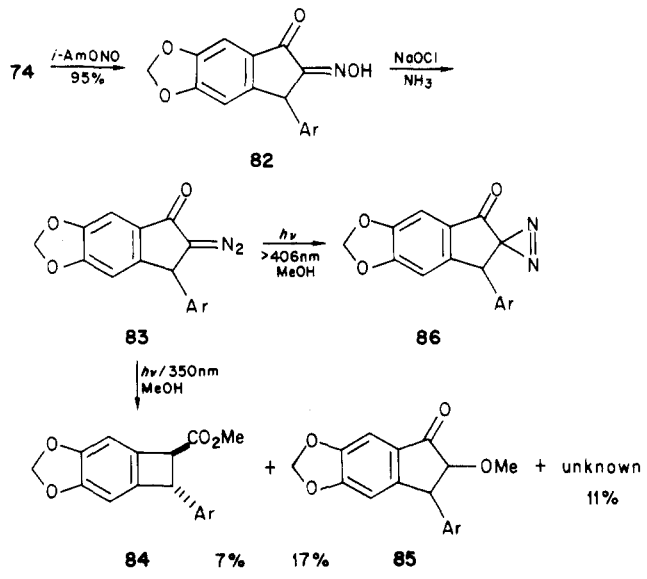
(36) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (b) Brook, A. G., Macrae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19. (c) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

Scheme XI



reasons: (1) Attack of the enolate or enol ether on the oxidizing agent would be expected to occur from the side opposite the large aryl group to give the trans arrangement of aryl and hydroxyl. (2) The 200-MHz ^{1}H NMR of **75** showed a coupling of 4.3 Hz for these two protons, more indicative of a trans relationship than a cis one.[37] Formation of the mesylate **76** was accomplished in 55% yield but was accompanied by the production of a second compound in 45% yield. These two compounds were easily separated by preparative HPLC. We have assigned the oxathiole structure **77** to this latter compound on the basis of its spectroscopic data, especially the ^{1}H and ^{13}C NMR spectra and the infrared spectrum which indicated the lack of the cyclopentanone carbonyl and the *S*-methyl group. This compound is presumably formed from **75** by base-catalyzed condensation of the methanesulfonyl unit onto the reactive carbonyl. The yield of **77** could be reduced by decreasing the amount of triethylamine used in the mesylation reaction. Addition of methyllithium to **76** produced the desired glycol monomesylate **78** in 41% yield. The cis stereochemistry of the oxygen functionalities is assigned by analogy to other organometallic additions to 2-substituted cycloalkanones and by the fact that no epoxide products were formed. When an aliquot of the reaction mixture was quenched with water after a short period of time, a 1:1 mixture of **78** and an isomer, presumably the stereoisomer resulting from addition cis to the mesylate, is formed. However, none of this latter compound is isolated if the reaction mixture is allowed to warm to 25 °C before workup. A small amount (18% NMR yield) of the dione **79** was also produced in this reaction, presumably by base-catalyzed elimination of methanesulfinic acid across the C–O bond via the lithium enolate of the indanone. This dione was also formed in 20% yield by sequential treatment of the ketol **75** with *n*-butyllithium and tosyl chloride, along with the expected tosylate in 41% yield. With the desired glycol monomesylate in hand, we could test the key arrangement of **78** to **80**. Treatment of **78** with potassium *tert*-butoxide in THF at 25 °C for 30 min effected complete destruction of starting material with the clean formation of a single product in quantitative yield. Unfortunately this product was not the desired ketone **80** but rather the indenol **81**, the product of a simple base-catalyzed elimination of the mesylate group. Presumably the system prefers to lose the fairly acidic benzhydryl proton and suffer β-elimination rather than undergo rearrangement to the strained dihydrobenzocyclobutene system **80**. No other reaction conditions could be found to rearrange **78** into **80**.

Scheme XII

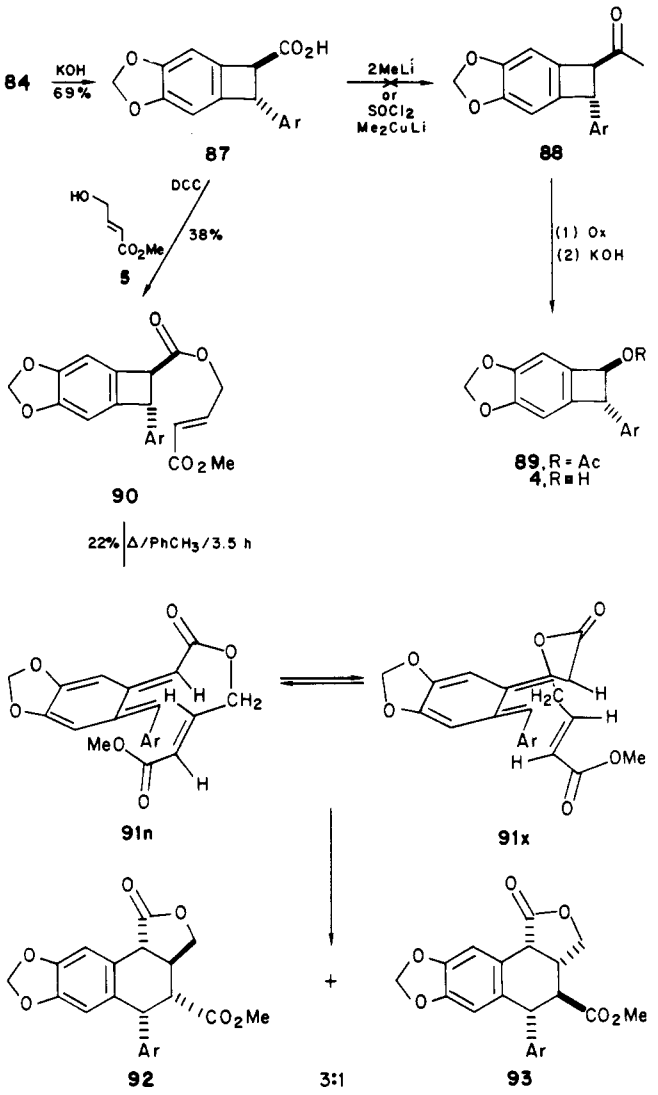


(b) Wolff Rearrangement. The final route to the benzocyclobutene proved successful albeit in very low yield in the key ring contraction step. The ketone **74** was converted into the diazo ketone **83** by way of the oxime **82** in 68% overall yield by a slight modification of the procedure of Cava.[38] Photolysis of a solution of **83** in deoxygenated methanol in a Rayonet apparatus (λ 350 nm) for 5 h at 25 °C resulted in a mixture of four products in poor yield. These could be separated by preparative TLC to give in order of elution: the desired dihydrobenzocyclobutene ester **84** in 7% yield, the starting indanone **74** (8%), the methoxyindanone **85** (17%), and an unknown compound (11%). In a separate experiment we showed that the ester **84** was itself photolabile under the reaction conditions, decomposing completely within 4 h of irradiation. Several other sets of reaction conditions (e.g., solvent, time, temperature) were attempted but the yield of **84** could not be increased. Since the ester **84** did not absorb light at wavelengths longer than 400 nm, we attempted to photolyze the diazo ketone **83** at long wavelength. When a Corning 3-74 filter (cutoff at 406 nm) was used, photolysis required 88 h at 0 °C to completely destroy the starting material. A single compound was produced in 60% yield in this reaction but its spectral data indicated that it was

(37) For example, the coupling constants for the protons at C4 and C5 of 2-cyclopenten-1-one are 2.2 Hz for the trans and 7.2 Hz for the cis. Therefore, it is most likely that the protons in **75** are trans. Anet, F. A. L.; Anet, R. In "Determination of Organic Structures by Physical Methods"; Nachod, F. C., Zuckerman, J. J., Eds.; Academic Press: New York, 1971; p 390.

(38) Cava, M. P.; Litle, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2757.

Scheme XIII



not the desired ester **84** but rather the diazirene **86**. The structure of **84** was assigned as trans due to the coupling constant of the cyclobutane protons which was 2.2 Hz. Blomquist and Bottomley[32] reported in similar compounds a coupling constant of 6.1 Hz for the cis isomer and 3.2 Hz for the trans. Moreover, when ester **84** was subjected to strongly basic hydrolysis conditions (10 N KOH in aqueous methanolic THF) overnight, no epimerization α to the carbonyl group was observed (based on the observed proton coupling constants). Therefore it is very likely that the ester in **84** is trans to the aryl group as desired.

The very low yield in the photolysis caused problems with succeeding steps in the synthesis since only small amounts of material were available. Hydrolysis of the ester **84** produced the acid **87** in 69% yield. We hoped to convert **87** into the methyl ketone **88** so that we could carry out a Baeyer–Villiger oxidation with retention of configuration to give the acetate **89** and thence the alcohol **4**. However, the two attempts at converting **87** into **88** failed: (1) treatment with 2 equiv of methyllithium; (2) conversion to the acid chloride with thionyl chloride followed by treatment with lithium dimethylcuprate.

Although the failure to produce **4** easily ended this synthetic approach to the epipodophyllotoxins, we decided to test the principle of an intramolecular Diels–Alder cycloaddition of a molecule similar to **7**. Therefore, DCC-promoted coupling of the acid **87** with the alcohol **5** was carried out to give the ester **90** in 38% yield. Refluxing

Table I. Chemical Shifts, Multiplicities, and Coupling Constants for Pentacyclic Lactones 92 and 93

	92		93	
proton	δ	multiplicity	δ	multiplicity
5	7.132 ppm	s	7.018 ppm	s
8	6.485	s	6.233	s
2′,6′	6.072	s	6.290	s
OCH_2O	5.969, 5.962, 5.943, 5.936	ABq	5.931, 5.924, 5.910, 5.903	ABq
11″	4.468	dd	4.150	d
1	4.461	d	4.016	d
11	4.164	d	4.398	dd
4	3.860	d	3.8	d
4′(OMe)	3.795	s	3.881	s
3′,5′(OMe)	3.739	s	3.856	s
CO_2Me	3.717	s	3.474	s
3	3.185	ddd	3.228	ddd
2	3.044	dd	2.836	dd

coupling constants	92	93
$J_{1,2}$	4.6	11.2
$J_{2,3}$	12.9	11.7
$J_{3,4}$	7.8	7.5
$J_{3,11}$	0	5.2
$J_{3,11''}$	5.3	0
$J_{11,11''}$	10.1	9.9

a toluene solution of **90** for 3.5 h followed by preparative TLC afforded in 22% yield a 3:1 mixture of the two lactones **92** and **93**, with the trans lactone **92** predominating. The structures were assigned by the spectroscopic data especially high-field ^1H NMR, as described in detail below. This result is very encouraging for the synthesis of **9n** from **7** as described earlier. Examination of molecular models of the two possible transition states for the reaction **91nx** indicates that the one leading to the trans lactone **92**, the endo transition state **91n**, is more strained than that leading to the cis lactone **93**, namely the exo transition state **91x**. However, in **91n** there is the possibility of favorable secondary orbital overlap which would lower the energy of this transition state compared to the exo-one **91x**. Therefore obtaining a 3:1 mixture of the trans and cis lactones implies that the favorable overlap outweighs the strain energy inherent in forming a trans five-membered lactone. Since the formation of a trans six-membered lactone or carbonate involves much less energy due to the reduced strain of the ring, these results would lead one to expect that the reaction of **7** would provide much more **9n** than **9x** and therefore be even more stereoselective for the synthesis of the necessary stereochemistry for podophyllotoxin **1**.

The assignment of the structures of the major and minor products **92** and **93** in this Diels–Alder reaction was based exclusively on high-field ^1H NMR data and on analogy to other assignments in the podophyllotoxin field in the literature.[39] The 200-MHz ^1H NMR spectra for the mixture of isomers and for the individual isomers are given in Figure 1. By careful preparative TLC, we were able to effect a partial separation of isomers and obtained a fraction comprising a 93:7 mixture of the major:minor isomers. The NMR spectrum of this partially purified material allowed us to assign all of the peaks of the major isomer. By then using a subtraction program on our data

(39) (a) Brewer, C. F.; Loike, J. D.; Horwitz, S. B.; Sternlicht, H.; Gensler, W. J. *J. Med. Chem.* **1979**, *22*, 215. (b) Gensler, W. J.; Murthy, C. D.; Trammell, M. H. *Ibid.* **1977**, *20*, 635. (c) Jardine, I.; Strife, R. J.; Kozlowski, J. *Ibid.* **1982**, *25*, 1077. (d) Rithner, C. D.; Bushweller, C. H.; Gensler, W. J.; Hoogasian, S. *J. Org. Chem.* **1983**, *48*, 1491. (e) Ayres, D. C.; Harris, J. A.; Jenkins, P. N.; Phillips, L. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1343.

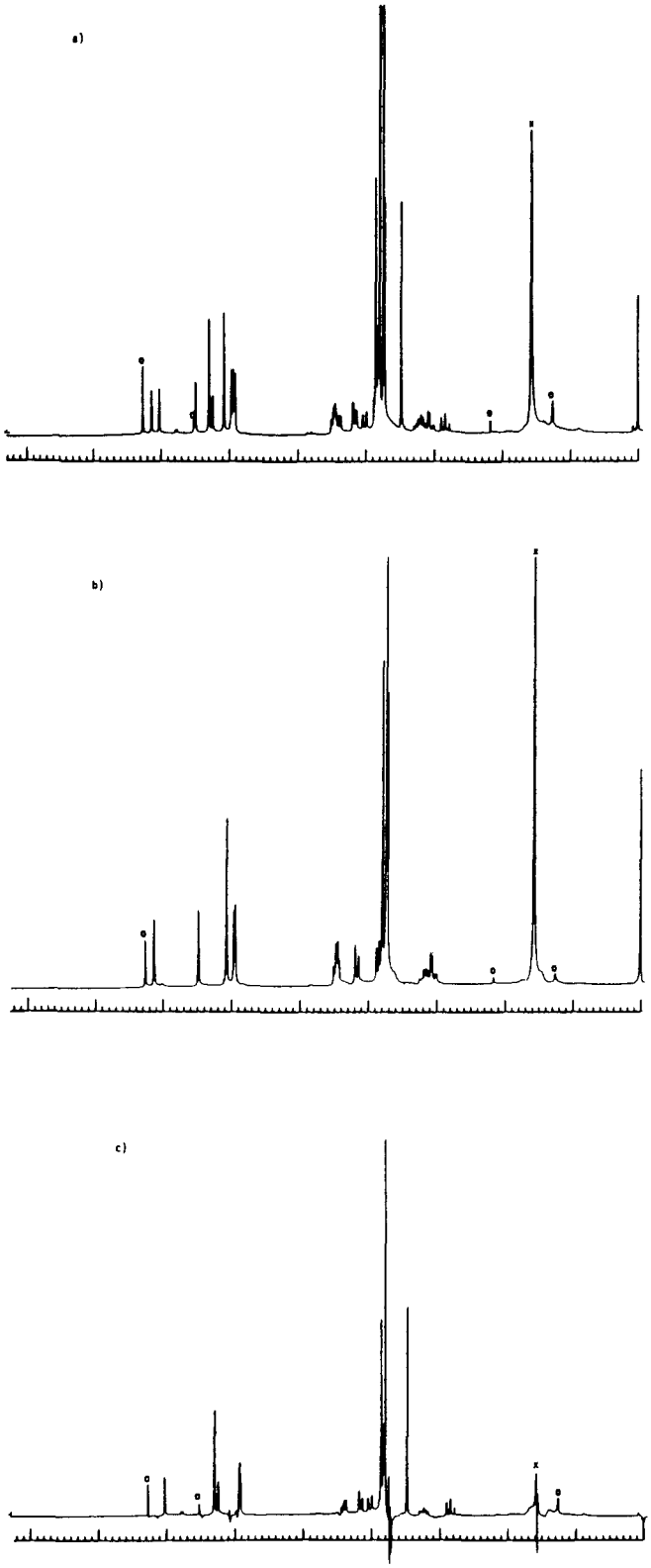
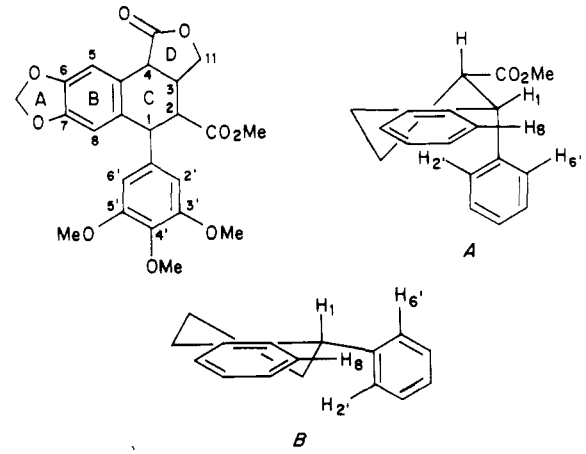


Figure 1. 200-MHz ^1H NMR spectra of the lactones **92** and **93** in $CDCl_3$: (a) 1:1 mixture; (b) trans lactone **92**; (c) cis lactone **93**. Peaks marked with x are due to water impurity and those with o are due to solvent impurities.

system, we were able to obtain a relatively clean spectrum of the minor isomer. A complete set of decoupling experiments were carried out to determine all of the multiplicities and coupling constants, as given in Table I. The basic argument for assigning the structures to the lactones involves the chemical shift differences of three protons in both isomers, namely H_1, H_8, and $H_{2'-6'}$. The chemical shift, multiplicity, and coupling constants for each proton in both isomers are given in Table I. Work in the literature, especially that of Brewer et al.[39a] has shown that when the tetrahydro aromatic ring (ring C) is in the half chair conformation A which forces the trimethoxyphenyl ring (ring E) to be pseudoaxial (e.g., podophyllotoxin, epipodophyllotoxin), it causes $H_{2'}$ and $H_{6'}$ to lie under the plane of the other aromatic ring (ring B) and the C2-carbonyl and thus to be *shielded*. The opposite is true for compounds which exist predominantly in the half-chair conformation B which allows ring E to be pseudoequatorial (e.g., picropodophyllotoxin), namely $H_{2'}$ and $H_{6'}$, do not lie in the shielding zone but more in the deshielding zone and thus are *deshielded*. The effect on H_8 is similar but in the opposite direction, namely H_8 lies above the plane of the E ring in conformation B and is thus *shielded* when compared to its position in conformation A. Finally, the chemical shift of H_1 is also affected by the conformation of the molecule. In conformation A it is pseudoequatorial and therefore lies more or less in the plane of the aromatic B ring and the C2-carbonyl group and thus should be *deshielded* somewhat with respect to its chemical shift in conformation B when it is pseudoaxial and is farther out of the plane of the B ring. Thus in conformational A one



would expect H_1 to be at *lower* field, H_8 to be at *lower* field, and $H_{2'-6'}$ to be at *higher* field than the corresponding protons in conformation B. This is the case for all of the known podophyllotoxin derivatives.[39] An examination of the chemical shifts of the protons of the major and minor isomers (Table I) show that in the major isomer H_1 and H_8 are at lower field and $H_{2'-6'}$ are at higher field than they are in the minor isomer. Thus the major isomer should exist in conformation A, which is a reasonable conformation only for the trans lactone **92**. The minor isomer should exist in conformation B, which is a reasonable conformation only for the cis lactone **93**. Additional support for these structural assignments can be found in the coupling constants between H_1 and H_2 ($J_{1,2}$) in both isomers (Table I). In the major isomer this coupling constant is 4.6 Hz while in the minor it is 11.2 Hz. These values (in conjunction with the Karplus vicinal correlation) imply that the dihedral angle H_1–C–C–H_2 is nearly 54° (or 126°) in the major isomer and on the order of 155° (or 25°) in the minor isomer. These relationships can only be true if the major isomer is the trans lactone **92** and the minor isomer the cis lactone **93**.

Thus although we were unable to prepare the desired substrate **7** for the synthesis of podophyllotoxin (**1**) by this route, we were able to successfully test the concept of utilizing the favorable secondary orbital overlap of a close analogue of **7**, namely **90**, to produce (via a stabilized endo transition state **91n**) predominantly the desired trans

lactone **92**. This compound has the correct relative stereochemistry at all four asymmetric centers as podophyllotoxin but without the oxygen functionality at the benzylic center and this work then comprises a stereoselective synthesis of this analogue of the natural system. We are currently attempting to prepare intermediates such as **8** and **91** by other routes, e.g., a Saegusa–Ito type of fragmentation, and thereby to prepare **1** by a very direct stereoselective route.

Experimental Section

General Methods. Proton nuclear magnetic resonance spectra (^{1}H NMR) were taken on a Varian T-60 or Bruker WP-200 spectrometer and are so indicated. Carbon NMR spectra (^{13}C NMR) were taken on an Varian CFT-20, Jeol FX90Q, or Bruker WP-200 spectrometer. All chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Infrared spectra (IR) were recorded on a Perkin–Elmer Model 710B or Model 137 infrared spectrophotometer as a liquid film or in a solution cell with polystyrene as a standard. Mass spectra (MS) were recorded on an AEI-MS9 or an AEI-MS25 spectrometer. Data reported are the m/e values for the most abundant peaks and are not a complete tabulation. Silica gel for chromatography was E. Merck silica gel 60 (70–230 mesh) and for flash chromatography was EM silica gel 9385 (230–400 mesh). Preparative high-pressure liquid chromatography (HPLC) was performed on a Waters Prep 500 instrument with silica gel cartridges and with ethyl acetate/hexane mixtures as eluent. Alumina for chromatography was EM neutral alumina 1077 (activity I) adjusted to the correct activity with water. All reagents and solvents were purified and distilled according to standard methods unless otherwise specified.

6-Bromopiperonal, 15. 6-Bromopiperonal was prepared by the method of Parijs,[40a] namely, by using bromine in acetic acid, but with the variation of adding a catalytic amount of iodine in carbon disulfide to the reaction mixture.[40b] In this manner a 60–70% yield of the crude bromide **15** could be obtained, which could be recrystallized from ethanol to give pure **15**: mp 127–129 °C [lit.[40b] mp 123 °C; 60 MHz ^{1}H NMR ($CDCl_3$) δ 10.15 (1 H, s), 7.35 (1 H, s), 7.13 (1 H, s), 6.10 (2 H, s).

5-Bromo-6-nitrobenzo-1,3-dioxole, 16. Concentrated nitric acid (250 mL) was cooled to 0 °C and with stirring 6-bromopiperonal (35 g, 0.153 mmol) was added in small portions over 2 h. The resulting yellow solution was poured onto 800 mL of ice water to precipitate a yellow solid. The solid was collected by filtration and washed well with water. Recrystallization from ethanol afforded 34 g (92%) of **16** as yellow needles: 60 MHz ^{1}H NMR ($CDCl_3$) δ 7.4 (1 H, s), 7.1 (1 H, s,), 6.1 (2 H, s).

5-Amino-6-bromobenzo-1,3-dioxole, 17. 5-Bromo-6-nitrobenzo-1,3-dioxole, **16** (3.4 g, 15 mmol), was added to a mixture of 100 mL of concentrated hydrochloric acid and 100 mL of acetic acid. With stirring at 0 °C zinc powder (25 g) was added in small portions over 1 h. After stirring an additional 15 min at 0 °C, concentrated ammonium hydroxide was added until the reaction mixture was slightly basic. After saturation with solid sodium chloride the reaction mixture was extracted with three 50-mL portions of methylene chloride. Drying (Na_2SO_4), decolorization with charcoal, and concentration by rotary evaporation afforded a solid which was recrystallized from aqueous ethanol to give 2.85 g (96%) of **17** as light brown needles: 60 MHz ^{1}H NMR ($CDCl_3$) δ 6.9 (1 H, s), 6.4 (1 H, s), 5.85 (2 H, s), 3.8 (2 H, bs).

5-Amino-6-bromobenzo-1,3-dioxole Hydrochloride. 5-Amino-6-bromobenzo-1,3-dioxole, **17**, was dissolved in 10 mL of ethanol and concentrated hydrochloric acid (10 mL) was added to precipitate fine needles. The solid was collected by filtration, washed with ethanol, and air dried to give 4.7 g (90%) of fine, grey needles of the hydrochloride of **17**.

6-Bromobenzo-1,3-dioxole-5-diazonium Tetrafluoroborate, 18. 5-Amino-6-bromobenzo-1,3-dioxole hydrochloride (0.92 g, 3.62 mmol) was suspended in 1.5 mL of water containing 1.5 mL of concentrated hydrochloric acid and the suspension was cooled to 0 °C. A solution of sodium nitrite (0.294 g, 4.25 mmol) in 2 mL of water was added dropwise over 5 min with stirring. The resulting yellow solution was stirred 5 min at 0 °C and then 48% aqueous fluoroboric acid (2 mL) was added all at once. A precipitate formed and the mixture was stirred for 30 min at 0 °C. The solid was collected by filtration, washed with cold ethanol, and finally air dried to give 0.97 g (85%) of the salt **18** as an off-white powder. Anal. Calcd for $C_7H_4N_2O_2BrVF_4$: C, 26.69; H, 1.26. Found: C, 26.69; H, 1.21.

5-Bromo-6-fluorobenzo-1,3-dioxole, 19a. The diazonium tetrafluoroborate **18** (1.7 g, 5.4 mmol) was dissolved in 100 mL of 48% fluoroboric acid. The solution was cooled with an ice–salt bath and irradiated with a 450-W Hanovia lamp with a Pyrex filter for 1 h. The crude product was filtered to remove an oily solid and the filtrate was neutralized with concentrated sodium hydroxide at 0 °C. The aqueous solution was extracted with methylene chloride and, after drying (Na_2SO_4) and concentration by rotary evaporation, afforded 0.15 g (13%) of **19a** as an oily solid: 60 MHz ^{1}H NMR ($CDCl_3$) δ 6.95 (1 H, d, J = 6 Hz), 6.7 (1 H, d, J = 6 Hz), 6.0 (2 H, s).

5-Bromo-6-iodobenzo-1,3-dioxole, 19b. 5-Amino-6-bromobenzo-1,3-dioxole hydrochloride (1.12 g, 4.45 mmol) was suspended in 1.5 mL of water containing 1.5 mL of concentrated hydrochloric acid. The suspension was cooled to 0 °C and solid sodium nitrite (0.31 g, 4.5 mmol) was added with stirring in small portions over 20 min. After an additional 10 min at 0 °C the green solution was poured with good stirring into 10 mL of water containing 3 g of potassium iodide. The aqueous mixture was extracted with methylene chloride and the methylene chloride solution was washed with aqueous sodium bisulfite. Drying (Na_2SO_4) and concentration by rotary evaporation afforded an orange oil which was purified by column chromatography on silica gel (60 g) with methylene chloride as eluent to give 1.3 g (90%) of **19b** as an orange solid: 60 MHz ^{1}H NMR ($CDCl_3$) δ 7.25 (1 H, s), 7.1 (1 H, s), 5.95 (2 H, s). Anal. Calcd for $C_7H_4O_2BrI$: C, 25.70; H, 1.22. Found: C, 25.85; H, 1.19.

5,8-Dihydro-5,8-epoxynaphtho[2,3-*d*]-1,3-dioxole, 20a. Using *n*-butyllithium: To a stirred solution of 5-bromo-6-iodobenzo-1,3-dioxole (**19b**) (0.3445 g, 1.06 mmol) and furan (1 mL) in 1 mL of THF at −78 °C under nitrogen was added 2.4 M *n*-butyllithium (0.44 mL, 1.06 mmol) dropwise via syringe. The addition was complete in 5 min and then the reaction mixture was stirred at −78 °C for 30 min. After warming to room temperature over 15 min, the reaction mixture was stirred for an additional 20 min and then poured into a mixture of water and methylene chloride. The methylene chloride solution was dried (Na_2SO_4) and concentrated by rotary evaporation to afford 0.39 g of a red oil. Preparative thin-layer chromatography on silica gel with 30% hexane in methylene chloride as eluent afforded 0.137 g (69%) of **20a** as a yellow solid: 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.15 (2 H, d, J = 1 Hz), 6.85 (2 H, s), 5.9 (2 H, m), 5.65 (2 H, d, J = 1 Hz); mass spectrum, m/e 188 (M^+).

Using magnesium: A solution of 5-bromo-6-iodobenzo-1,3-dioxole (**19b**) (100 mg, 0.32 mmol) in dry THF (1 mL) and furan (2 mL) were introduced into a dry 25-mL round-bottom flask. Magnesium (30 mg, 1.25 mg atom), which had been cleaned by suspending in methyl iodide, was added to the solution. The reaction mixture was then heated to reflux under nitrogen and the magnesium darkens giving a white precipitate. After 3 h, more THF/furan was added to the reaction mixture. The reaction mixture was heated to reflux for 18 h and then allowed to cool. The suspension was filtered through Celite with dichloromethane: the filtrate was concentrated to leave a deep red oil which solidifies during evaporation of solvent under high vacuum to give 53 mg of **20a** (88%).

5,8-Dihydro-5,8-methanonaphtho[2,3-*d*]-1,3-dioxole, 20b. Magnesium (400 mg) was suspended in a solution of 10% methyl iodide in THF. The magnesium was immediately added to a solution of 5-bromo-6-iodobenzo-1,3-dioxole (**19b**) (0.3 g, 0.975 mmol) and cyclopentadiene (1 mL, freshly distilled) in 1.5 mL of THF. The mixture was refluxed under nitrogen for 12 h. The clear, yellow solution gradually became a yellow, milky suspension. The solution was diluted with methylene chloride and washed with saturated aqueous sodium chloride. The solution was dried (Na_2SO_4) and concentrated by rotary evaporation to afford 0.21 g of a yellow oil. The crude product mixture was separated by

(40) (a) Parijs, A. H. *Recl. Trav. Chim. Pays-Bas* **1930**, *49*, 17. (b) Dallacker, F. *Liebigs Ann. Chem.* **1960**, *633*, 14.

preparative chromatography on silica gel with 1:1 pentane:methylene chloride as eluent. The second fastest moving band afforded 25 mg (14%) of the adduct **20b**: 60 MHz ^{1}H NMR ($CDCl_3$) δ 6.75 (1 H, m), 5.8 (2 H, m), 3.7 (2 H, m), 3.2 (2 H, m); mass spectrum, m/e 186 (M^+).

5-Acetoxy-5,6-dihydrocyclobuta(*f*)-1,3-benzodioxole, 21. A suspension of 6-aminobenzo-1,3-dioxole-5-carboxylic acid (300 mg, 1.66 mmol) in warm vinyl acetate (5 mL) was added concurrently with isoamyl nitrite (240 mg, 2.1 mmol) to refluxing vinyl acetate (7 mL) over 15 min. More vinyl acetate is added to redissolve any precipitated acid. On completion of addition, the solution was refluxed for a further 30 min. The reaction was allowed to cool to 25 °C and was concentrated in vacuo to leave a dark brown liquid which solidifies on standing. The solid was taken up in chloroform and filtered. The filtrate was concentrated to leave a dark red liquid which was purified by preparative TLC with silica gel as support and benzene as eluent. The least polar fraction afforded 29 mg (8%) of the desired adduct **21**: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.752 (1 H, s), 6.642 (1 H, s), 5.901 (2 H, s), 5.753 (1 H, d, J = 4.2 Hz), 3.472 (1 H, dd, J = 4.2, 14.2 Hz), 3.046 (1 H, d, J = 14.2 Hz), 2.095 (3 H, s).

α-Cyano-6-bromobenzo-1,3-dioxole-5-propanoic Acid, 26. 6-Bromopiperonal (**15**) (12.6 g, 55 mmol) was placed in a 200-mL round-bottom flask equipped with a Dean–Stark trap with cyanoacetic acid (4.4 g, 51 mmol), ammonium acetate (500 mg, 6.5 mmol), pyridine (11 mL), and benzene (50 mL), the reaction mixture was heated to reflux until the requisite amount of water (0.9 mL) was collected, and the reaction mixture allowed to cool. A yellow solid precipitates out, is collected, and dried under vacuum. The pyridine salt (19.0 g) was carried on without purification.

A suspension of the pyridine salt (5.0 g, 13.3 mmol) in saturated sodium bicarbonate solution (200 mL) was warmed to 80–85 °C until the salt had dissolved. Sodium borohydride (1.40 g, 36 mmol) was then carefully added portionwise at such a rate that the reaction remained controllable. Once all the reducing agent had been added the reaction mixture was heated at 80–85 °C for a further 30 min, after which time it was allowed to cool a little and dilute hydrochloric acid added dropwise until the pH of the solution was 2. The reaction mixture was then allowed to stand at room temperature for 2–3 h during which time the cyano acid **26** precipitated. The acid was filtered and then dried in vacuo to leave a pale yellow solid which could be recrystallized from benzene/THF to give 3.4 g (87%) of **26**: mp 160–161 °C (softens at 140 °C); 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.022 (1 H, s), 6.868 (1 H, s), 6.007 (2 H, s), 3.86 (1 H, dd, J = 9.8, 5.9 Hz), 3.41 (1 H, dd, J = 14.2, 5.9 Hz), 3.10 (1 H, dd, J = 14.2, 9.8 Hz).

6-Bromobenzo-1,3-dioxole-5-propanonitrile, 27. A suspension of the cyano acid **26** (100 mg, 0.34 mmol) in dry dimethylacetamide (0.5 ml) was heated at 170 °C in an oil bath (preheated to that temperature) for 15 min. The pale brown solution was poured onto water (10 mL) and the aqueous phase goes milky white. It was allowed to stand overnight at room temperature whereupon a pale brown solid precipitated. This was collected, washed with water and pentane, and then dried under reduced pressure. Recrystallization from ethanol yielded 60 mg (71%) white needles: mp 79–81 °C; 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.999 (1 H, s), 6.775 (1 H, s), 5.968 (2 H, s), 2.981 (2 H, t, J = 7.3 Hz), 2.617 (2 H, t, J = 7.3 Hz); IR ($CHCl_3$) 2250 cm^{-1}. Anal. Calcd for $C_{10}H_8NO_2Br$: C, 47.26; H, 3.15. Found: C, 47.23; H, 3.11.

5-Cyano-5,6-dihydrocyclobuta(*f*)-1,3-benzodioxole, 28. Ammonia (350 ml) was condensed and dried over potassium (~0.5 g) until the blue color persists and then redistilled into a second flask. A very small piece of potassium was added to ammonia to insure that it is still dry with the liquid *immediately* going blue and the color persisting. Once satisfied that the solvent was dry, potassium hydride (1.9 g, 47.3 mmol) in *o*-xylene is added. One or two crystals of ferric nitrate are also added. The solution is stirred until it goes colorless suggesting the formation of potassium amide (this period can vary, it may occasionally be necessary to add another crystal or two of ferric nitrate). The reaction mixture is stirred for a further 30 min after decolorization. The nitrile **27** (3.0 g, 11.8 mmol) was then added to the reaction mixture in 1-g portions every minute and the reaction mixture is stirred for a further 5–6 min. The reaction mixture goes a green/brown color immediately on addition of the nitrile. Once the reaction is complete it is quenched by careful addition of ammonium chloride (2.54 g, 47.3 mmol) and the excess ammonia allowed to evaporate. Water (300 mL) was then added to the residue and the aqueous phase extracted with chloroform (3 × 100 mL) and the solution dried (Na_2SO_4). The dry solution was filtered, the solvent removed under reduced pressure, and the residue subjected to column chromatography on silica gel with chloroform as eluent. The product was recrystallized from ethanol to give 1.3 g (80%) of **28** as a white solid: mp 84–85 °C; 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.684 (1 H, s), 6.604 (1 H, s), 5.881 (2 H, s), 4.053 (1 H, dd, J = 5.1, 2.7 Hz), 3.482 (1 H, dd, J = 13.7, 5.1 Hz), 3.328 (1 H, dd, J = 13.7, 2.7 Hz). Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.05. Found: C, 69.25; H, 3.98.

5-Cyano-5-(phenylthio)-5,6-dihydrocyclobuta(*f*)-1,3-benzodioxole, 29. A solution of benzene thiol (23.1 g, 21 mmol) in petroleum ether (35–60 °C, 100 mL) was cooled in an ice bath to 0 °C and sulfuryl chloride (32.4 g, 24 mmol) added dropwise over 1 h to the reaction mixture, with vigorous stirring. The reaction mixture becomes a white solid which gradually goes to a red liquid. The ice bath was removed after a further hour and the reaction mixture stirred for an additional hour at ambient temperature. The red solution was concentrated and then distilled under reduced pressure. The resultant product, benzenesulphenyl chloride, is a red liquid and should be stored under an argon atmosphere in the freezer.

A solution of the nitrile **28** (1.2 g, 6.94 mmol) in dry THF (20 mL) was introduced into a dry 50-mL, three-neck round-bottom flask (flame dried under vacuum and flushed with nitrogen) and cooled to −78 °C in a dry ice/acetone bath and stirred for 15 min. *n*-Butyllithium (Ventron, 2.55 M, 2.75 mL, 7.01 mmol) was added and the solution, which changes to an orange/yellow color, was stirred at −78 °C for 15 min. Freshly distilled (bp 95–100 °C (12.5 mm)) benzenesulfenyl chloride (1 g, 6.95 mmol) was then added to the reaction mixture via a syringe and the reaction stirred at −78 °C for 45 min. The cold bath is then removed and the reaction mixture stirred at ambient temperature for 1 h. The yellow-orange color gradually darkens to a deep green. When dilute hydrochloric acid (10%, 2 mL) was then added to quench the reaction, the dark color immediately disappears and the orange-yellow color is regenerated. The reaction is stirred for a further 20 min, whereupon it is poured onto ether (75 mL) and water (20 mL) added. The two phases were separated and the aqueous phase further extracted with ether (2 × 50 mL). The organic extracts were combined, washed with dilute acid (1 × 25 mL) and water (2 × 25 mL), and then dried (Na_2SO_4). The dry solution is filtered and the solvent is removed under reduced pressure to leave a red residue which was subjected to column chromatography on silica gel as support with a 9:1 ratio of petroleum ether:ether as eluent to give 1.7 g (87%) of **29** as a red oil: 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.68–7.40 (5 H, m), 6.651 (1 H, s), 6.343 (1 H, s), 5.91 (2 H, ABq), 3.838, 3.76, 3.479, 3.411 (2 H, ABq, J = 13.7 Hz).

6*H*-Cyclobuta(*f*)-1,3-benzodioxol-5-one, 31, and the Cyanohydrin, 30. The thiophenoxy nitrile **29** (220 mg, 0.73 mmol) was dissolved in aqueous acetonitrile (25%) (6 mL) with *N*-bromosuccinimide (354 mg, 20 mmol) and stirred under nitrogen for 1.5 h. The color of the reaction changes from yellow to orange during this time. The reaction mixture was poured onto ether (75 mL) and extracted with water (2 × 25 mL). The aqueous layer was extracted with ether (2 × 50 mL) and the ether extracts combined and dried (Na_2SO_4). The dry ethereal solution was filtered and concentrated under reduced pressure; the residue was a pale yellow solid which was purified by preparative thin-layer chromatography with silica gel as support and ether:petroleum ether (1:3) as eluent. The chromatogram gave two products, the less polar product (22 mg, 20%) being the desired ketone **31** and the more polar (60 mg, 43%) being the cyanohydrin **30**. The cyanohydrin **30** (60 mg) was added to a solution of 2 N sodium hydroxide (2 mL) and aqueous acetonitrile (25%) (2 mL) and stirred under nitrogen for 45 min. The reaction mixture goes from pale yellow to deep red. The solution is poured onto ether (50 mL) and separated. The ethereal phase was washed with water (2 × 25 mL) and the combined aqueous extracts were, in turn, washed with ether (2 × 25 mL). The organic extracts were combined and dried (Na_2SO_4). After filtration and concentration of the dried solution, the product was purified by preparative

thin-layer chromatography with the same support and solvent as above to give 47 mg (39%) of **31**: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.95 (1 H, s), 6.87 (1 H, s), 6.05 (2 H, s), 3.83 (2 H, s); IR (liquid film) 1770–1780 cm^{-1}.

6-Bromo-6*H*-cyclobuta(*f*)-1,3-benzodioxol-5-one, 23. The cyclobutenone **31** (54 mg, 0.33 mmol) was dissolved in dry carbon tetrachloride (4 mL) and recrystallized *N*-bromosuccinimide (64 mg, 0.36 mmol) added to the solution along with a catalytic amount of benzoyl peroxide (~10 mg). The reaction mixture was heated to reflux for 30 min under a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to leave a pale yellow residue. The residue was purified by preparative thin-layer chromatography with silica gel as support and benzene as eluent to give 37 mg (47%) of **23** as a white solid: 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.040 (1 H, s), 6.790 (1 H, s), 6.132 (2 H, s), 5.820 (1 H, s); IR (liquid film) 1770–1780 cm^{-1}; mass spectrum, *m/e* 242, 240 (M^+, 70%), 161 ($M^+ - 81$, $M^+ - 79$, 41%), 133 ($M^+ - 109$, $M^+ - 107$, 100%).

3,4,5-Trimethoxybromobenzene, 32, from the Phenol 34. When the literature procedure of Foley[26d] was followed, 154 g (1.00 mol) of 2,6-dimethoxyphenol **34** (Aldrich), 0.4 g (0.01 mol) of sodium hydride (Alfa, 60% in mineral oil), and 11.5 mL (0.28 mol) of anhydrous MeOH (distilled over MeONa) in 1.5 L of anhydrous chloroform (distilled over CaH_2) was treated with 188.7 g (1.06 mol) of *N*-bromosuccinimide at −45 to −35 °C to give, after workup, 145.6 g [62% recrystallized yield (lit. 61%)] of white crystals, mp 93–100 °C (lit.[26b] mp 99.5–100 °C). The product, 4-bromo-2,6-dimethoxyphenol, was pure enough to be carried onto the next reaction.

A mixture of 132.1 g (0.567 mol) of 4-bromo-2,6-dimethoxyphenol and 55.5 g (1.39 mol) of NaOH in 1.5 L of H_2O was cooled to 10 °C and 80.4 mL (0.851 mol) of dimethyl sulfate was added. The mixture was refluxed for 3 h and an equal amount of dimethyl sulfate (total 1.70 mol) was then added. The mixture was refluxed for another 3 h. TLC analysis showed no starting material. Upon cooling overnight, the gray product solidified and was filtered off and dissolved in 2 L of ether. The ether solution was filtered to remove 1.9 g of impurity and washed sequentially with 1 × 5% NaOH solution, 2 × water, and 1 × brine. The ether phase was dried with anhydrous calcium chloride and evaporated to give 119 g of off-white solid which was recrystallized in 450 mL of hexane to give 105.1 g of **32** as a solid, mp 78–81 °C. Upon concentration of the mother liquor to 150 mL, a second crop of 7.6 g of solid was obtained, mp 78–80 °C. The total yield of **32** was 80%. The product was pure enough to be carried onto the next step.

***cis*-8-Bromobicyclo[4.2.0]octa-1,3,5-trien-7-ol, 36a.** Sodium borohydride (20 mg, 0.7 mmol) was added to a solution of ketone **35** (100 mg, 0.5 mmol) in ethanol (4 mL) and the resultant solution was stirred at room temperature for 30 min. The reaction was quenched by adding aqueous ammonium chloride (1 mL) and water (5 mL), the reaction mixture was then poured onto ether (30 mL) and the two layers separated. The aqueous extract was twice more washed with ether (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4). The product was filtered and concentrated to give 81 mg (81%) of the alcohol **36a** as a white solid which was used without further purification: 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.40–7.10 (4 H, m), 5.80 (1 H, d, J = 5 Hz), 5.40 (1 H, d, J = 5 Hz); ^{13}C NMR ($CDCl_3$) δ 146.9, 144.1, 131.0, 130.8, 128.5, 123.7, 73.5, 56.7; mass spectrum, *m/e* (70 eV) 200, 198 (M^+, 1.8%), 119 ($M^+ - 81$, $M^+ - 79$, 100%), 91 ($M^+ - 109$, $M^+ - 107$, 66.5%); IR ($CDCl_3$) 3575 cm^{-1}.

***cis*-8-Bromo-7-[(*tert*-butyldimethylsilyl)oxy]bicyclo-[4.2.0]octa-1,3,5-triene, 36b.** A solution of the alcohol **36a** (93 mg, 0.470 mmol), *tert*-butyldimethylsilyl chloride (86 mg, 0.56 mmol), and imidazole (81 mg, 1.2 mmol) in dry dimethylformamide (2 mL) was stirred under nitrogen overnight and then warmed to 35 °C for 3 h. The reaction mixture was poured onto ether (50 mL), water (10 mL) was added, and the two layers separated. The aqueous phase was further extracted with ether (3 × 30 mL). The organic extracts were combined and dried (Na_2SO_4). The solution was filtered and the solvent removed *in vacuo* to leave a pale yellow oil which was purified by preparative thin-layer chromatography on silica gel with benzene as eluent to give 124 mg (84%) of the pure silyl ether as a colorless oil: 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.40–7.15 (4 H, m), 5.6 (2 H, ABq, J = 5 Hz), 0.98 (9 H, s), 0.19 (3 H, s), 0.18 (3 H, s); IR ($CDCl_3$) 1280 cm^{-1}.

Ethyl 2-(Bromomethyl)benzoate, 37. The bromo ketone **35** (100 mg, 0.5 mmol) was stirred overnight in ethanol (3 mL) in the presence of potassium carbonate (350 mg, 2.5 mmol) under an atmosphere of nitrogen. The solution was filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel as support and benzene as eluent. The least polar component afforded 47 mg (38%) of the benzoate **37**: 60 MHz ^{1}H NMR ($CDCl_3$) δ 8.1–7.85 (1 H, m), 7.6–7.3 (3 H, m), 5.0 (2 H, s), 4.45 (2 H, q, J = 7 Hz), 1.4 (3 H, t, J = 7 Hz); mass spectrum, *m/e* (16 eV) 244, 242 (M^+, 14%), 163 ($M^+ - 81$, $M^+ - 79$, 77%), 135 ($M^+ - 109$, $M^+ - 107$, 100%).

Benzyltriphenylphosphonium Bromide, 41. Benzyl bromide (3 g, 17.5 mmol) and triphenylphosphine (4.6 g, 17.5 mmol) were added to benzene (30 mL) and the solution heated to reflux overnight. The phosphonium salt **41** precipitates out of solution during this time as a white solid. The reaction mixture was allowed to cool and the white solid filtered. The solid was then dried on the pump overnight to give 7.2 g (95%) of **41** which was used without further purification.

(*E*)- and (*Z*)-6-Bromo-5-(2-phenylethenyl)benzo-1,3-dioxole, 42(*EZ*). The salt **41** (4.2 g, 9.7 mmol) was placed in dry THF (50 mL) and the suspension cooled to 0 °C in a dry 200-mL three-necked round-bottom flask. *n*-Butyllithium (9.8 mmol) was then syringed into the cooled suspension. The reaction mixture went immediately yellow and then turned to a red solution once all the salt had reacted. A further 20 mL of THF was added to dissolve the ylide. The solution was stirred for 1 h and then transferred to an addition funnel by means of a double headed needle. The ylide solution was then added dropwise to a solution of bromopiperonal **15** (2.5 g, 9 mmol) in dry benzene. Initially the color is discharged immediately but the final reaction mixture is a dark red solution. The reaction mixture was then left to stir at ambient temperature for 2 h. The reaction was then poured into ether (200 mL) and water (100 mL) added. The two layers were separated and the aqueous layer further extracted with ether (2 × 100 mL). The ethereal extracts were dried (Na_2SO_4), filtered, and concentrated to leave an oil which was a mixture of the *E* (**42(*E*)**) and *Z* (**42(*Z*)**) isomers. The two isomers could be separated on the Waters 500 HPLC (after a short column filtration to remove $Ph_3P{=}O$) with 2% ethyl acetate/hexane. Although the *Z* isomer **42(*Z*)** was obtained pure in 41% yield, the *E* isomer **42(*E*)** (50%) was slightly contaminated with **42(*Z*)**. On a large scale beginning with 12 g (52.4 mmol) of **15**, an 89% yield was obtained.

42(*Z*): 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.15 (5 H, s), 7.00 (1 H, s), 6.60 (1 H, s), 6.50 (2 H, s), 5.80 (2 H, s).

42(*E*): 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.60–6.65 (9 H, m), 5.85 (2 H, s).

Isomerization of 42(*Z*) to 42(*E*). The reaction product from the Wittig reaction after removal of $Ph_3P{=}O$, which is a mixture of the two olefins **42(*ZE*)**, was dissolved in carbon tetrachloride and a few crystals of iodine added. The solution was stirred until only the *E* isomer was visible in the ^{1}H NMR. The reaction is complete when only one methylenedioxy peak at δ 5.95 is visible in the ^{1}H NMR. The reaction was worked up by washing with solid sodium thiosulfate (2 × 50 mL), water (2 × 50 mL), and drying (Na_2SO_4).

(*E*)-6-Bromo-5-(2-phenyl-1,2-epoxyethyl)benzo-1,3-dioxole, 43. The olefin **42(*E*)** (200 mg, 0.66 mmol) was dissolved in dichloromethane (20 mL) and sodium carbonate (76 mg, 0.77 mmol) was added and the suspension cooled in an ice bath to 0 °C. *m*-Chloroperbenzoic acid (126 mg, 0.77 mmol) was added and the reaction mixture stirred overnight. A further 0.5 equiv of *m*-chloroperbenzoic acid (63 mg, 0.38 mmol) was added and the reaction mixture stirred for a further 2 h. The reaction mixture was filtered and the filtrate washed with saturated sodium thiosulfate (2 × 25 mL), saturated sodium carbonate (2 × 25 mL), and water (2 × 25 mL) and dried (Na_2SO_4). The solution was filtered and concentrated to leave a yellow oil which solidified under high vacuum to give 169 mg (80%) of **43**: 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.35 (5 H, s), 7.00 (1 H, s), 6.80 (1 H, s), 5.95 (2 H, s), 3.95 (2 H, ABq, J = 10 Hz).

Reaction of Epoxide 43 with *n*-Butyllithium/Magnesium Bromide: Formation of 5-Phenyl-5,6-dihydrocyclobuta-

(f)-1,3-benzodioxol-5-ol, 44. Modifying the procedure of Durst[28] for *o*-bromophenyl epoxides, a solution of 476 mg (1.49 mmol) of epoxide **43** in 25 mL of dried THF was stirred at −78 °C under nitrogen. A solution of magnesium bromide (2.54 M, 1.47 mL, 3.73 mmol) in ether was added slowly. The cloudy solution was stirred for 10 min and 0.722 mL (1.79 mmol) of 2.48 M *n*-butyllithium was added dropwise to give an intense yellow solution. The solution was stirred at −78 °C for 15 min and warmed up to 25 °C over a period of 50 min. The color of the solution turned deep burgundy and then changed to light brown as the temperature approached 0 °C. The reaction was quenched with saturated ammonium chloride solution and extracted three times with ether. The combined ethereal phase was washed with water and dried with $MgSO_4$ to give 393 mg of light brown oil. The ^1H NMR spectrum showed the presence of 33% of dihydrobenzocyclobutenol **44**, 5% of ketone **45**, and 28% of starting material.

Benzocyclobutenol **44**: yellow oil; 200 MHz ^1H NMR ($CDCl_3$) δ 7.50–7.25 (5 H, m), 6.76 (1 H, s), 6.72 (1 H, s), 5.925, 5.919, 5.916 5.910 (2 H, ABq, J = 1.2 Hz), 3.496, 3.428, 3.408, 3.341 (2 H, ABq, J = 13.7 Hz); IR (neat) 3400 (s) cm^{-1}; mass spectrum (70 eV), m/e 240 (41, M^+), 238 (84), 163 (31), 105 (32), 86 (59), 84 (100), 77 (77).

Ketone **45**: 200 MHz ^1H NMR ($CDCl_3$) δ 8.10–7.20 (5 H, m), 6.72 (3 H, bs), 5.87 (2 H, bs), 4.17 (2 H, s); IR (neat) 1680 (s) cm^{-1}; mass spectrum (70 eV), m/e 240 (33, M^+), 135 (36), 105 (100), 77 (49), 51 (21); high-resolution mass spectrum, m/e 240.0766, calcd for $C_{15}H_{12}O_3$ 240.0786.

When *n*-BuLi was added before the magnesium bromide, the same result was observed. When boron trifluoride etherate was used in place of magnesium bromide, a complex reaction mixture resulted.

Isomerization of 43 To Give 46 and 47. Magnesium (170 mg, 6.9 mol) was added to dry ether (3 mL) under an atmosphere of nitrogen. Dibromoethane (1.18 g, 6.3 mmol) was then syringed with the reaction mixture. Heat is evolved as magnesium bromide is formed. After a while two layers appear; the lower layer was removed and syringed into a solution of the epoxide **43** in dry ether (20 mL) also under nitrogen. The epoxide **43** was left to stir for 1.5 h. Once the reaction is over the reaction mixture is quenched by adding saturated ammonium chloride, and the reaction mixture was then poured onto ether (30 ml), extracted with water (2 × 10 mL), and dried (Na_2SO_4). The solution was filtered, concentrated, and purified by column chromatography on silica gel with benzene as eluent. The first quick chromatography gave a 3:1 mixture of products **46** and **47** in 80% yield. A second more careful chromatography gave pure **46** as the least polar product with an impure sample of **47** also being obtained.

Compound **46**: 60 MHz ^1H NMR ($CDCl_3$) δ 9.80 (1 H, s), 7.4–7.1 (5 H, m), 7.00 (1 H, s), 6.50 (1 H, s), 5.90 (2 H, s), 5.30 (1 H, s).

Compound **47**: 60 MHz ^1H NMR ($CDCl_3$) δ 7.85–8.05 (2 H, m), 7.1~7.5 (4 H, m), 6.5 (1 H, s), 5.85 (2 H, s), 4.28 (2 H, s).

Rearrangement of Benzocyclobutenol 44 to 6-Methylbenzo-1,3-dioxol-5-yl Phenyl Ketone, 48. A sample of benzocyclobutenol **44** in Me_2SO-d_6 was treated with a little crushed NaOH for 0.5 h. Water was added and the solution was extracted three times with ether. The ether phase was washed three times with water, once with brine, and evaporated to give exclusively ketone **48**: 200 MHz ^1H NMR ($CDCl_3$) δ 7.90–7.35 (5 H, m), 6.82 (1 H, s), 6.75 (1 H, s), 5.98 (2 H, s), 2.28 (3 H, s); IR (neat) 1650 (s) cm^{-1}.

***(EZ)*-1-(6-Bromobenzo-1,3-dioxol-5-yl)-2-[(*tert*-butyldimethylsilyl)oxy]styrene, 49.** The aldehyde **46** (160 mg, 0.5 mmol) was dissolved in 10 mL of diethyl ether and 2 mL of THF in a one-neck round-bottom flask capped by a serum cap with a nitrogen gas inlet and was cooled to −98 °C in a liquid nitrogen/methanol slush bath under a nitrogen atmosphere. *tert*-Butyllithium (260 uL of 2.1 M solution, 0.55 mmol) was added via cooled syringe. Immediately on addition of the alkyllithium, the reaction underwent a color change from colorless to purple to orange. The mixture was stirred at −98 to −90 °C for 1.5 h, and then *tert*-butyldimethylsilyl chloride (76 mg, 0.5 mmol) was added. The cooling bath was removed and the reaction was allowed to stir for 3 h as it warmed to ambient temperature. Aqueous ammonium chloride was added, and the reaction was poured into water, extracted with ether (3 × 30 mL), and dried (Na_2SO_4). After evaporation of the solvent in vacuo, the residue was subjected to preparative TLC on silica gel with benzene as eluent. The least polar fraction was collected and shown to be the silyl enol ether **49**. No other products could be identified.

α-(3,4,5-Trimethoxyphenyl)-6-bromobenzo-1,3-dioxole-5-methanol, 50. A solution of 35.0 g (142 mmol) of aryl bromide **32** in 600 mL of dried THF was cooled to −78 °C under nitrogen and 62.6 mL (2.49 M solution, 156 mmol) of *n*-butyllithium was added dropwise with stirring over a period of 25 min. The solution was allowed to stir for another 45 min at −78 °C and a solution of 34.1 g (149 mmol) of 6-bromopiperonal **15** in 400 mL of dried THF was added at a relatively fast rate over a period of 30 min. After stirring at −78 °C for 1.5 h, the solution was allowed to warm up to 25 °C for 2 h. The brown solution was quenched with saturated ammonium chloride solution. Most of the THF was removed in vacuo and water was added. The product was extracted with methylene chloride, washed twice with water, dried with $MgSO_4$, and evaporated in vacuo to give 56.9 g of solid. The desired benzyhydrol **50** was isolated by Waters 500 HPLC (SiO_2, 2 columns, hexane–ethyl acetate (70:30)) and recrystallized (ethyl acetate/hexane) to give 21.0 g (37%) of light yellow crystals: mp 137–140 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 6.962 (1 H, s), 6.939 (1 H, s), 6.619 (2 H, s), 6.034 (1 H, bs), 5.941, 5.935, 5.920, 5.913 (2 H, ABq, J = 1.3 Hz), 3.801 (6 H, s), 3.796 (3 H, s), 3.029 (1 H, bs); IR ($CDCl_3$) 3400 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{17}O_6Br$: C, 51.40; H, 4.28. Found: C, 51.65; H, 4.34.

Attempts to improve the yield by inverse addition or use of a Grignard were not successful.

6-Bromobenzo-1,3-dioxol-5-yl 3,4,5-Trimethoxyphenyl Ketone, 51. A solution of 214 mg of crude benzhydrol **50** in 2.5 mL of acetone was cooled below −20 °C in an Erlenmeyer flask with a magnetic stirrer. A solution of 0.2 mL (0.54 mmol) of 2.7 M chromium trioxide[41] in dilute sulfuric acid was added dropwise. After 0.5 h, the mother liquor was decanted and the green precipitate was ground and washed with acetone. The combined acetone solution was neutralized with $NaHCO_3$ and the solvent removed by evacuation in vacuo. Water was added and the product was extracted three times with methylene chloride, washed three times with water, and evaporated to give 153 mg of brown oil. The desired benzophenone **51** was isolated by column chromatography (silica gel, methylene chloride as eluent) to give 91 mg (41% based on bromide **32**) of yellow crystal: mp 155–158 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 7.10 (2 H, s), 6.85 (1 H, s), 6.64 (1 H, s), 6.08 (2 H, s), 3.98 (6 H, s), 3.92 (3 H, s).

5-[1-(3,4,5-Trimethoxyphenyl)-1,2-epoxyethyl]-6-bromobenzo-1,3-dioxole, 52. When Corey's procedure[29] was followed, 6.77 mmol of yellow dimethylsulfonium methylide in 23 mL of Me_2SO and 5 mL of THF was prepared at ice/salt temperature and a solution of 2.14 g (5.42 mmol) of benzophenone **51** in 20 mL of THF/Me_2SO (1:1) was added. The mixture turned brick-red in color, was stirred for 2 min, and warmed up to 25 °C for 1 h. The reaction was quenched with three volumes of water to give a yellow solution. The product was extracted four times with ether, washed three times with water and once with brine, dried (K_2CO_3), and evaporated in vacuo to give 2.20 g (97%) of the pure epoxide **52** as a yellow oil. It could be crystallized from pentane/ether to give pale yellow solid: mp 105–107 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 6.99 (1 H, s), 6.95 (1 H, s), 6.47 (2 H, s), 5.96 (2 H, s), 3.77 (3 H, s), 3.76 (6 H, s), 3.26 (2 H, s); IR (neat) 1595 (s), 1450 (bs), 1400 (s), 1315 (s), 1220 (s), 1110 (s), 1015 (s) cm^{-1}; mass spectrum (70 eV), m/e 410 (27, M^+), 408 (27, M^+), 381 (31), 379 (33), 300 (100), 299 (39), 269 (84), 227 (36); high-resolution mass spectrum, m/e 410.0199, calcd for $C_{18}H_{17}O_6Br^{81}$ 410.0189; 408.0218, calcd for $C_{18}H_{17}O_6Br^{79}$ 408.0208. Anal. Calcd for $C_{18}H_{17}O_6Br$: C, 52.82; H, 4.16. Found: C, 52.88; H, 4.15.

α-(3,4,5-Trimethoxyphenyl)-6-bromobenzo-1,3-dioxole-5-acetaldehyde, 53. To a solution of 2.10 g (5.13 mmol) of epoxide **52** in 225 mL of dry ether at 25 °C under a nitrogen atmosphere was added dropwise 1.03 mL (2.57 mmol) of 2.5 M magnesium bromide in ether. The solution turned turbid and was allowed to stir for 0.5 h. It was poured into water, washed four times with water, and once with brine, dried (Na_2SO_4), and evaporated to give 2.04 g (97% crude yield) of reasonably pure aldehyde **53** (by

(41) Eisenbraun, E. J. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5, p 310.

(42) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3249.

^{1}H NMR >92% pure) as a white solid. The solid could be recrystallized from hexane/ethyl acetate to yield 1.3 g (62%) of fine white crystals: mp 134–135 °C; 200 MHz ^{1}H NMR ($CDCl_3$) δ 9.94 (1 H, bs), 7.06 (1 H, s), 6.59 (1 H, s), 6.40 (2 H, s), 5.97 (2 H, s), 5.30 (1 H, bs), 3.82 (9 H, s); IR (neat) 2825 (w), 1720 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{17}O_6Br$: C, 52.82; H, 4.16. Found: C, 52.95; H, 4.13.

The rearrangement also occurred in THF except at a much slower rate ($t_{1/2}$ = 3 days). Aldehyde **53** was poorly soluble in ether (0.26 g/100 mL at 0 °C).

6-[(3,4,5-Trimethoxyphenyl)methyl]benzo-1,3-dioxole-5-carboxaldehyde, 56. When the procedure of Durst[28] was modified, 146 mg (0.357 mmol) of epoxide **52** and 59.7 mg (0.393 mmol) of *tert*-butyldimethylsilyl chloride were dissolved in 10 mL of anhydrous ether and cooled to −78 °C under a nitrogen atmosphere. To this clear solution was added 0.286 mL (0.714 mmol) of 2.5 M magnesium bromide in ether, followed by *tert*-butyllithium (0.397 mL of 1.89 M solution, 0.750 mmol) in pentane. The resulting yellow solution was allowed to stir for 30 min at −78 °C and became a brown mixture. It was warmed to 25 °C for 1 h and quenched with saturated ammonium chloride solution. The reaction mixture was extracted three times with ether, washed twice with water, dried with $MgSO_4$, and evaporated in vacuo to give 135 mg of a yellow oil. The oil was purified by preparative TLC (silica gel, 3.5:1 hexane/ethyl acetate as eluent) to give 21 mg (18%) of aldehyde **56**. No silylated benzocyclobutenol was obtained.

Aldehyde **56**: 200 MHz ^{1}H NMR ($CDCl_3$) δ 10.162 (1 H, s), 7.353 (1 H, s), 6.694 (1 H, s), 6.337 (2 H, s), 6.057 (2 H, s), 4.294 (2 H, s), 3.818 (3 H, s), 3.797 (6 H, s); IR (neat) 1680 (s) cm^{-1}; mass spectrum (70 eV), *m/e* 330 (M^+, 100), 301 (M − CHO, 10), 299 (42), 282 (26), 268 (21), 149 (38), 134 (28); high-resolution mass spectrum, *m/e* 330.1096, calcd for $C_{18}H_{18}O_6$ 330.1103.

In the product mixture, approximately 5–10% of the debrominated aldehyde corresponding to **53** was also observed by ^{1}H NMR. Attempts to increase the yield of aldehyde **56** or obtain benzocyclobutenol by using THF as solvent, trimethylaluminum or boron trifluoride etherate in place of magnesium bromide, or omitting the silyl halide were not successful. Control reactions showed that at −78 °C the epoxyaryl anion was stable toward magnesium bromide for at least 30 min. Rearrangement of the epoxyaryl anion occurred to an extent of 84% at −63 to −58 °C for 15 min. When trimethylsilyl chloride was used instead of the *tert*-butyl analogue and added 10 min after the addition of *tert*-butyllithium at −78 °C, no silylated benzocyclobutenol was observed.

Reaction of Aldehyde 53 with Trimethylsilyl Iodide and *tert*-Butyllithium. To a solution of 100 mg (0.244 mmol) of aldehyde **53** in 7 mL of dry THF at −78 °C under a nitrogen atmosphere was added 0.0365 mL (0.257 mmol) of trimethylsilyl iodide (distilled over CaH_2). The yellow solution was stirred at −78 °C for 1.5 h and cooled to −98 °C. A solution of *tert*-butyllithium (0.246 mL of a 2.08 M solution, 0.512 mmol) in pentane was added dropwise. The resulting deep burgundy solution was stirred at −98 °C for 3 h and warmed up to −78 °C for another 3 h. The solution was warmed up to 25 °C for 45 min and quenched with saturated ammonium chloride solution. The mixture was extracted three times with ether. The ether layer was washed three times with water and once with brine and evaporated in vacuo to give 103 mg of a complicated mixture as a yellow oil. Preparative TLC (hexane–ethyl acetate, 5:1, R_f 0.55) gave 14 mg (14%) of an unknown oil: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.735 (1 H, s), 6.730 (2 H, s), 6.460 (2 H, s), 5.923 (2 H, s), 4.010 (2 H, s), 3.819 (9 H, s), 0.043 (6 H, s); IR (neat) 2945 (s), 1582 (s), 1470 (bs), 1320 (s), 1235 (s), 1120 (s), 1030 (s), 1000 (m), 920 (m), 860 (m), 830 (s) cm^{-1}; mass spectrum (70 eV), *m/e* 404 (M^+, 10), 302 (22), 301 (100), 269 (4).

α-(3,4,5-Trimethoxyphenyl)-6-bromobenzo-1,3-dioxole-5-acetaldehyde Dimethyl Acetal, 57. To a solution of 561 mg (1.37 mmol) of aldehyde **53** and 0.210 mL (1.92 mmol) of trimethyl orthoformate in 20 mL of dry methanol and 1.5 mL of dry benzene under a nitrogen atmosphere was added two crystals of *p*-toluenesulfonic acid. The solution was heated at 50 °C for 44 h. TLC indicated that there was still starting material. More trimethyl orthoformate (0.15 mL) and catalyst were added. After another 6 h at 50 °C, water was added and the mixture neutralized with $NaHCO_3$. The organic phase was separated, washed with saturated $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, and evaporated to give 710 mg (100%) of the acetal **57** (pure by ^{1}H NMR) as a light yellow gum. Attempts to crystallize the gum were not successful: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.96 (1 H, s), 6.92 (1 H, s), 6.55 (2 H, s), 5.90 (2 H, s), 4.90, 4.80, 4.70, 4.60 (2 H, ABq, *J* = 6 Hz), 3.80 (6 H, s), 3.78 (3 H, s), 3.36 (3 H, s), 3.33 (3 H, s); IR (neat) 1585 (s), 1500 (s), 1470 (bs), 1230 (s), 1050 (bs), 1030 (s), 1000 (m), 950 (w), 920 (m), 890 (w), 780 (m) cm^{-1}.

(*EZ*)-1-(Benzo-1,3-dioxol-5-yl)-2,3′,4′,5′-tetramethoxystyrene, 58. To a solution of 78 mg (0.171 mmol) of acetal **57** in 5 mL of dry ether under a nitrogen atmosphere at −78 °C was added 0.134 mL (0.342 mmol) of 2.54 M magnesium bromide in ether and *tert*-butyllithium (0.202 mL of 2.08 M solution, 0.419 mmol) in pentane. The resulting orange brown mixture was stirred at −78 °C for 45 min and refluxed for 5 days. The reaction was quenched with saturated ammonium chloride solution. The organic layer was washed twice with water, dried with $MgSO_4$, and evaporated in vacuo to give 67 mg of brown oil. The oil was subjected to preparative TLC to give 31 mg (53% yield) of a 2:1 isomeric mixture of enol ethers **58**: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.98 (1 H, bs), 6.80 (1 H, bs), 6.70 (1 H, s), 6.62 (1 H, s), 6.43 (1 H, s), 6.34 (1 H, s), 5.94 (2 H, s), 3.86 (3 H, bs), 3.80 (6 H, bs), 3.75 (3 H, bs); IR (neat) 2920 (m), 1630 (w–m), 1580 (s), 1470 (bs), 1225 (s), 1120 (s), 1030 (s), 1000 (m), 925 (m), 800 (w) cm^{-1}; mass spectrum (70 eV), *m/e* 344 (M^+, 100), 329 (73), 301 (28), 298 (15), 157 (11), 149 (23), 135 (14), 75 (18).

2-(6-Bromobenzo-1,3-dioxol-5-yl)dithiane, 61. 6-Bromopiperonal **15** (5 g, 22 mmol), 1,3-propanedithiol (2.46 g, 23 mmol), and a catalytic amount of *p*-toluenesulfonic acid were added to dry benzene (60 mL) and the apparatus connected to a Dean–Stark trap. The reaction mixture was heated to reflux overnight and then allowed to cool to room temperature. The solvent was removed in vacuo to leave a yellow solid which was recrystallized from benzene/hexane to give 6.4 g (90%) of white crystals: mp 116–117 °C; 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.10 (1 H, s), 6.90 (1 H, s), 6.00 (2 H, s), 5.40 (1 H, s), 3.10–2.80 (4 H, m), 2.21–1.95 (2 H, m). Anal. Calcd for $C_{11}H_{11}O_2BrS_2$: C, 41.39; H, 3.45. Found: C, 41.52; H, 3.49.

2-Deuterio-2-(6-deuteriobenzo-1,3-dioxol-5-yl)dithiane, 62a. The dithiane **61** (300 mg, 0.94 mmol) in dry THF (3 mL) was introduced into a dry three-neck 25-mL round-bottom flask (flame dried under vacuum and nitrogen), the solution cooled to −40 °C, and *tert*-butyllithium (2.625 mL of 1.2 M solution, 3.2 mmol) added. The reaction mixture immediately goes dark brown and was stirred at −40 °C for 1.5 h, then warmed to room temperature, and stirred for a further 20 min once the reaction mixture had reached room temperature. Deuterium oxide (2 mL) was added to quench the reaction and stirred for a further 15 min. The reaction was poured onto ether and the layers separated. The aqueous layer was extracted with ether (3 × 50 mL) and the combined ethereal extracts dried (Na_2SO_4). The solution was filtered and then concentrated to leave a sweet smelling brown oil which was purified by preparative TLC on silica gel with benzene as eluent to give 167 mg (74%) of the dideuterated product **62a** as an oil. ^{1}H and ^{2}H NMR indicated that this compound was contaminated with a small amount of the monodeuterated product **62b**: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.99 (1 H, s), 6.95 (0.1 H, d), 6.76 (1 H, t), 5.96 (2 H, s), 3.045 (2 H, dt, *J* = 3.5, 14 Hz), 2.89 (2 H, dt, *J* = 14, 3.5 Hz), 2.16 (1 H, d of irregular pentet, *J* = 14 Hz), 1.91 (1 H, qt, *J* = 14, 3.5 Hz); ^{2}H NMR ($CHCl_3$) δ 6.96 (1 D, s), 5.10 (1.25 D, s).

2-[6-(*N*,*N*-Diisopropylamino)benzo-1,3-dioxol-5-yl]dithiane, 63. Dry THF (5 mL) was introduced into a 50-mL three-neck round-bottom flask previously flame-dried under vacuum and under nitrogen. Dry diisopropylamine (175 mg, 1.73 mmol) was added to the solvent and the solution cooled to −78 °C and stirred for 15 min. *n*-Butyllithium (790 mL of 2.3 M solution, 1.82 mmol) was injected into the cooled solution and the reaction mixture stirred for 15 min at −78 °C and 15 min at room temperature. While at room temperature the reaction mixture goes a pale yellow color. The LDA solution was cooled to −78 °C and a solution of the dithiane **61** (500 mg, 1.57 mmol) in dry THF (5 mL) was added by syringe in one portion. The reaction mixture darkens to an orange-brown color. The reaction was kept at −78 °C for 2 h and then allowed to come to room temperature over a further 3 h. The

color changes to dark red over this time. The reaction was quenched by adding deuterium oxide to the reaction mixture and then pouring onto water (10 mL). The aqueous phase was extracted with ether (3 × 30 mL) and then dried (Na_2SO_4). After filtering and concentrating under reduced pressure, the crude reaction product was purified by preparative TLC with silica gel as support and benzene as eluent to give 54 mg (10%) of a compound assigned the structure **63** as the major isolable product: 200 MHz ^1H NMR ($CDCl_3$) δ 7.138 (1 H, s), 6.687 (1 H, s), 5.972 (1 H, s), 5.945 (2 H, s), 3.405 (2 H, septet, J = 6.3 Hz), 3.054 (2 H, td, J = 14, 4 Hz), 2.848 (2 H, dt, J = 14, 4 Hz), 2.15 (1 H, dm, J = 14 Hz), 1.90 (1 H, qt, J = 14, 4 Hz), 1.072 (6 H, d, J = 6.3 Hz), 0.959 (6 H, d, J = 6.3 Hz): mass spectrum (70 eV), m/e 339 (M^+, 12.4), 2.96 (M^+ - 43, 52), 233 (M^+ - 106, 42), 218 (M^+ - 121, 78), 190 (M^+ - 149, 28.3), 189 (M^+ - 150, 25.8), 188 (M^+ - 151, 100), 187 (M^+ - 152, 28.7), 176 (M^+ - 163, 38.4), 175 (M^+ - 164, 20.2), 174 (M^+ - 165, 22.9), 160 (M^+ - 179, 21.6).

6-Bromobenzo-1,3-dioxole-5-carboxaldehyde Dimethyl Acetal, 64. Two crystals of *p*-toluenesulfonic acid were added to a solution of 3.10 g (13.5 mmol) of 6-bromopiperonal **15** and 2.22 mL (20.3 mmol) of trimethyl orthoformate in 20 mL of dry methanol and 40 mL of dry benzene under a nitrogen atmosphere. After stirring for 1 h at 25 °C, ether and water were added. The organic phase was washed three times with water and once with brine and evaporated to give 3.7 g (100%) of pure acetal **64** which solidified on cooling. An analytical sample was prepared by recrystallization from hexane: mp 39–40 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 7.04 (1 H, s), 6.96 (1 H, s), 5.93 (2 H, s), 5.41 (1 H, s), 3.40 (6 H, s); IR (neat) 1475 (s), 1410 (m), 1240 (s), 1110 (s), 1090 (s), 1030 (s), 980 (m) cm^{-1}.

α-(3,4,5-Trimethoxyphenyl)-6-(dimethoxymethyl)benzo-1,3-dioxole-5-methanol, 66.[10b,c] To a solution of the acetal **64** (3.08 g, 11.2 mmol) in 50 mL of dry THF at −78 °C under a nitrogen atmosphere was added dropwise *tert*-butyllithium (11.0 mL of a 2.08 M solution, 23.0 mmol) in pentane over a period of 15 min. The light brown solution was stirred at −78 °C for 1 h and 3,4,5-trimethoxybenzaldehyde (**65**) (2.67 g, 13.7 mmol) in 30 mL of dry THF was added over a period of 15 min. The mixture was stirred for 2.5 h at −78 °C and warmed to 25 °C for 2.5 h. The reaction was quenched with saturated ammonium chloride solution and extracted three times with ether. The ether phase was washed three times with water and once with brine, dried over $MgSO_4$, and evaporated to give 4.8 g of crude benzhydrol **66** as a yellow gum. The material was recrystallized in ethanol to give 3.4 g (77%) of **66** as pale yellow crystals: mp 123–125 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 7.13 (1 H, s), 6.77 (1 H, s), 6.70 (2 H, s), 6.17 (1 H, d, J = 5 Hz), 6.00 (2 H, s), 5.55 (1 H, s), 3.87 (3 H, s), 3.85 (6 H, s), 3.43 (3 H, s), 3.33 (3 H, s); IR (neat) 3400 (bm), 2900 (s), 1580 (s), 1470 (bs), 1220 (s), 1105 (s), 1010 (s), 920 (m), 860 (m) cm^{-1}.

Attempted Preparation of Mesylate or Halides of Benzhydrol 66: 5-Methoxy-7-(3,4,5-trimethoxyphenyl)-5,7-dihydrofuro[3,4-*f*]benzo-1,3-dioxole, 68, and 6-[Methoxy-(3,4,5-trimethoxy)methyl]benzo-1,3-dioxole-5-carboxaldehyde, 69. Via PBr_3. A solution of the benzhydrol **66** (72 mg, 0.184 mmol) and dry pyridine (0.0149 mL, 0.184 mmol) in 2 mL of dry THF was treated with *n*-butyllithium (0.0824 mL of 2.34 M solution, 0.193 mmol) in hexane under a nitrogen atmosphere at −78 °C for 15 min. To this solution was added PBr_3 (0.006 mL, 0.0693 mmol, distilled over CaH_2) and the solution stirred at −78 °C for 2.5 h, followed by warming to 25 °C over a period of 1.25 h. The mixture was poured into cold $NaHCO_3$ solution and extracted twice with methylene chloride. The organic phase was washed three times with water and once with brine, and evaporated in vacuo to give 83 mg of yellow oil. The oil was subjected to preparative TLC (hexane/ethyl acetate, 1.5:1) to give 10 mg (10% recovery) of starting material (R_f 0.3) and 46 mg (69% yield) of ketal **68** (R_f 0.5): 200 MHz ^1H NMR ($CDCl_3$) δ 6.86 (1 H, s), 6.70 (2 H, s), 6.53 (1 H, s), 6.13 (1 H, s), 6.02 (1 H, s), 5.99 (1 H, s), 5.97 (1 H, s), 3.86 (9 H, s), 3.60 (3 H, s); IR (neat) 2920 (bm), 1595 (s), 1460 (s), 1335 (s), 1125 (s), 1035 (s), 1005 (s), 970 (m), 840 (m), 795 (w) cm^{-1}; mass spectrum (70 eV), m/e 360 (M^+, 15), 329 (37), 328 (81), 313 (100), 177 (19), 73 (23), 55 (34).

When the reaction mixture was allowed to remain at 0 °C for 2 days, ^1H NMR showed the presence of 37% ketal **68** and 22% aldehyde **69**.

Via Mesylate/LiBr. A solution of benzhydrol **66** (121 mg, 0.309 mmol) in 3 mL of dry THF at −78 °C under a nitrogen atmosphere was treated with 139 mL of *n*-butyllithium (0.139 mL of 2.34 M solution, 0.324 mmol) in hexane for 15 min. To this solution was added methanesulfonyl chloride (0.0239 mL, 0.309 mmol distilled over CaH_2) and the yellow mixture stirred at −78 °C for 1 h, followed by warming to −23 °C over a period of 1 h. The mesylate solution was transferred via a double-ended needle to a mixture of lithium bromide (269 mg, 3.09 mmol, oven dried) in 4 mL of HMPA (distilled over CaH_2) and 1 mL of dry THF at −23 °C. The mixture was stored at −23 °C for 1 day and one half of it was worked up by pouring into cold $NaHCO_3$ solution. The mixture was extracted three times with ether and the ether phase washed four times with cold water and once with cold brine and evaporated in vacuo to give 67 mg of a colorless oil which decomposed upon drying under vacuum to a brown oil. The oil was subjected to preparative TLC (hexane/ethyl acetate, 2:1) to give 30 mg (54%) of aldehyde **69** (R_f 0.40). No ketal **68** was obtained.

Aldehyde **69**: 200 MHz ^1H NMR ($CDCl_3$) δ 10.35 (1 H, s), 7.35 (1 H, s), 7.05 (1 H, s), 6.61 (2 H, s), 6.07 (2 H, s), 6.05 (1 H, s), 3.83 (9 H, s), 3.40 (3 H, s); IR (neat) 2920 (m), 1680 (s), 1602 (m), 1590 (s), 1500 (s), 1475 (s), 1250 (s), 1110 (s), 1030 (s), 1000 (w), 920 (w), 795 (w) cm^{-1}.

Attempts to isolate the mesylate or to prepare the chloride with lithium chloride or thionyl chloride gave varying amounts of aldehyde **69**. The reaction with triphenylphosphine/carbon tetrachloride gave ketal **68**. Attempts to react the unisolated bromide with activated magnesium or *n*-butyllithium also gave aldehyde **69**.

A standard sample of aldehyde **69** was prepared by the acid (1% HCl) hydrolysis of the O-methylated acetal in THF at 25 °C for a few minutes. This acetal was prepared by the treatment of acetal **66** with potassium hydride in THF/DMF (1:1) followed by quenching with methyl iodide: 200 MHz ^1H NMR ($CDCl_3$) δ 7.15 (1 H, s), 6.97 (1 H, s), 6.68 (2 H, s), 5.98 (2 H, s), 5.67 (1 H, s), 5.55 (1 H, s), 3.85 (9 H, s), 3.40 (3 H, s), 3.37 (3 H, s), 3.32 (3H, s); IR (neat) 2900 (s), 1595 (s), 1480 (bs), 1250 (s), 1100 (bs), 1015 (m), 995 (m), 940 (w), 885 (w), 800 (w), 725 (w) cm^{-1}.

Methyl β-Oxobenzo-1,3-dioxole-5-propanoate, 71. When the procedure of Hajos[42] was modified, a mixture of 61.9 g (1.55 mmol) of 60% sodium hydride in mineral oil and 71 mL (0.387 mmol) of 25% potassium hydride in mineral oil was washed three times with dry THF (total 1.5 L) under a nitrogen atmosphere in a 3-L three-neck round-bottom flask fitted with a reflux condenser and an addition funnel. A solution of 0.5 L of dry THF and 130 mL (1.546 mmol) of dimethyl carbonate (dried with $CaCl_2$) was added and the mixture was heated at 66 °C while a solution of 126.8 g (0.773 mmol) of acetopiperone **70** (prepared by the method of Robinson[33b] in 77% overall yield) in 1 L of dry THF was added slowly. After the addition, the brown solution with white precipitate was heated for 1 h. After cooling, the excess metal hydride was destroyed with methanol and the mixture neutralized with acetic acid. The solvent was evaporated and the mixture extracted three times with methylene chloride. The organic phase was washed twice with a $NaHCO_3$ solution, dried with $MgSO_4$, and evaporated in vacuo to give 170.3 g (99%) of pure β-keto ester **71** as a yellow solid: mp 82–86 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 7.51 (1 H, dd, J = 8.0, 2.0 Hz), 7.38 (1 H, d, J = 2.0 Hz), 6.83 (1 H, d, J = 8.0 Hz), 6.04 (2 H, s), 3.93 (2 H, s), 3.73 (3 H, s); IR ($CDCl_3$) 1725 (s), 1675 (s) cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.50. Found: C, 59.36; H, 4.52.

Methyl α-[(3,4,5-Trimethoxyphenyl)methylene]-β-oxobenzo-1,3-dioxole-5-propanoate, 72. A mixture of the β-keto ester **71** (169 g, 0.759 mmol), 3,4,5-trimethoxybenzaldehyde (**65**) (133 g, 0.676 mmol), glacial acetic acid (19.8 mL, 0.345 mmol), and piperidine (6.8 mL, 0.069 mmol) in 2.8 L of benzene (dried with $CaCl_2$) in a 5-L round bottom flask fitted with a Dean–Stark trap was heated at reflux. More acetic acid (11 mL) was added and TLC showed no starting material after 19 h. The cooled mixture was washed twice each with 5% HCl, 5% NaOH, and brine, dried with $CaCl_2$, filtered through silica gel, and evaporated to give 298 g (100%) of crude ester **72** as a brown gum which resisted crystallization: 200 MHz ^1H NMR ($CDCl_3$) δ 7.86 (1 H, s), 7.58 (1 H, d, J = 8.0 Hz), 7.50 (1 H, s), 6.83 (1 H, d, J = 8.0 Hz), 6.63 (2 H, s), 6.04 (2 H, s), 3.80 (3 H, s), 3.73 (3 H, s), 3.66

(6 H, s); IR (neat) 1720 (s), 1660 (s) cm^{-1}. Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.00. Found: C, 62.78; H, 5.14.

Methyl 6,7-Dihydro-5-oxo-7-(3,4,5-trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxole-6-carboxylate, 73. Modifying the procedure of Vecchionacci,[34] a solution of the crude ester **72** (276 g, 0.689 mol) in 7 L of methylene chloride (distilled over CaH_2) was cooled to 0 °C under a nitrogen atmosphere and stirred mechanically. To this solution was added $AlCl_3$ (101 g, 0.759 mol) over a period of 10 min. After 1 h of stirring at 0 °C, the reddish brown mixture was poured into ice containing concentrated HCl. The product was extracted twice with methylene chloride, washed with 5% $NaHCO_3$ solution, and precipitated out as a yellow solid by stirring with 5% NaOH. The solid was filtered through glass wool, acidified with dilute HCl, and extracted twice with methylene chloride. The organic phase was evaporated in vacuo to give 216 g (78%) of **73** as a yellow solid: mp 152–158 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 7.144 (1 H, s), 6.651 (1 H, s), 6.326 (2 H, s), 6.095 (1 H, s), 6.087 (1 H, s), 4.784 (1 H, d, J = 4.4 Hz), 3.835 (3 H, s), 3.816 (3 H, s), 3.799 (6 H, s), 3.688 (1 H, d, J = 4.4 Hz); IR (neat) 1735 (s), 1700 (s) cm^{-1}. Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.00. Found: C, 63.07; H, 4.92.

6,7-Dihydro-7-(3,4,5-trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one, 74. To a solution of the crude β-keto ester **73** (216 g, 539 mmol) in 2.5 L of acetone was added 300 mL of 50% aqueous HCl. The solution was heated at reflux for 2 days. The resulting brown solution was neutralized with $NaHCO_3$ and evaporated to remove most of the acetone. A solution of 5% HCl in water was added and the mixture extracted twice with methylene chloride. The organic phase was washed with 5% NaOH solution, twice with water, and once with brine, dried over $MgSO_4$, passed through silica gel (1:1 methylene chloride–diethyl ether), and evaporated in vacuo to give 179 g (97%) of **74** as a light yellow solid, mp 170–173 °C. Recrystallization from ethanol did not improve the purity significantly: mp 171–175 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 7.131 (1 H, s), 6.636 (1 H, s), 6.302 (2 H, s), 6.063 (1 H, s), 4.350 (1 H, dd, J = 7.4, 3.4 Hz), 3.823 (3 H, s), 3.794 (6 H, s), 3.180 (1 H, dd, J = 9.1, 7.4 Hz), 2.655 (1 H, dd, J = 9.1, 3.4 Hz); IR (neat) 1700 (s) cm^{-1}; mass spectrum (70 eV), m/e 342 (M^+, 100), 341 (8), 327 ($M^+ - CH_3$, 9), 314 ($M^+ - CO$, 0.8), 311 ($M^+ - CH_3O$, 13), 267 (5), 71 (5); high-resolution mass spectrum (70 eV), m/e 342.1116, calcd for $C_{19}H_{18}O_6$ 342.1104. Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.67; H, 5.24. Found: C, 66.67; H, 5.23.

Indanone **74** could also be prepared in 76% yield from ester **73** in one step following the procedure of Vecchionacci[34] (0 °C, 0.5 h) for analogous compounds.

Preparation of Silyl Enol Ether of Ketone 74. A solution of LDA in 50 mL of THF was prepared by reacting *n*-butyllithium (21.2 mL of 1.52 M solution, 32.2 mmol) in hexane with diisopropylamine (5.32 mL, 38.0 mmol) at 0 °C. The solution was cooled to −78 °C and the indanone **74** (10.0 g, 29.2 mmol) in 500 mL of THF was added slowly. After 0.5 h at −78 °C, a solution of trimethylsilyl chloride [6.31 mL, 49.7 mmol, distilled over CaH_2 and treated with 1.79 mL (12.9 mmol) of dry triethylamine] in 20 mL of THF was added to the orange reaction mixture. The resulting light orange solution was warmed to 25 °C overnight. The solvent was removed and the product dissolved in cold methylene chloride. The organic phase was washed with cold 5% $NaHCO_3$ solution, dried over $MgSO_4$ and $CaSO_4$, and evaporated in vacuo to give 12.2 g (100%) of the crude silyl enol ether as a yellow foam: 200 MHz ^1H NMR ($CDCl_3$) δ 6.834 (1 H, s), 6.683 (1 H, s), 6.360 (2 H, s), 5.910 (1 H, d, J = 1.3 Hz), 5.900 (1 H, d, J = 1.3 Hz), 5.435 (1 H, d, J = 2.4 Hz), 4.340 (1 H, d, J = 2.4 Hz), 3.808 (3 H, s), 3.790 (6 H, s), 0.334 (9 H, s); IR (neat) 2920 (s), 1580 (s), 1450 (s), 1330 (s), 1240 (s), 1105 (s), 1030 (s), 900 (m), 850 (s), 720 (m) cm^{-1}.

***trans*-6,7-Dihydro-6-hydroxy-7-(3,4,5-trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one, 75. Via Silyl Enol Ether.** To a mechanically stirred solution of the above silyl enol ether (11.8 g, 28.4 mmol) in 200 mL of methylene chloride at 0 °C was added 150 mL of cold 5% $NaHCO_3$ solution, followed immediately by a cold solution of *m*-chloroperbenzoic acid (7.5 g, 36.9 mmol, 85%) in 200 mL of methylene chloride. After stirring for 15 min at 0 °C, more peracid was added when TLC showed the presence of starting material. After a total of 30 min at 0 °C, the solution was warmed to 25 °C overnight. The organic phase was washed with 5% Na_2CO_3, dried over $MgSO_4$, and evaporated in vacuo to give 7.8 g of yellow foam. The foam was chromatographed on a Waters HPLC (2 columns, 30% ethyl acetate in methylene chloride, R_f 0.22) to give 2.4 g (24%) of the alcohol **75** as a light yellow solid: mp 183–186 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 7.128 (1 H, s), 6.618 (1 H, s), 6.445 (2 H, s), 6.096 (1 H, d, J = 1.0 Hz), 6.077 (1 H, d, J = 1.0 Hz), 4.416 (1 H, d, J = 4.3 Hz), 4.100 (1 H, d, J = 4.3 Hz), 3.848 (3 H, s), 3.822 (6 H, s), 3.682 (1 H, bs); IR (neat) 3400 (bs), 1705 (s) cm^{-1}.

The chromatography also yielded 1.4 g (14%) of starting indanone **74**.

Via MoOPH Reaction. When the same preparation for the above silyl enol ether was followed, *n*-butyllithium (9.55 mL of 1.52 M solution, 14.5 mmol) in hexane, diisopropylamine (2.22 mL, 15.8 mmol) in 50 mL of THF, and the indanone **74** (4.5 g, 13.2 mmol) in 250 mL of THF were reacted and cooled to −22 °C. Through a side arm under a nitrogen atmosphere was added MoOPH[35] (8.7 g, 19.9 mmol) in one portion. The mixture turned from yellow to green to blue in color. After 20 min at −22 °C, 50 mL of saturated 5% $NaHCO_3$ was added and stirred for 20 min at 25 °C. Most of the THF was evaporated and methylene chloride was added. The organic phase was washed once with 5% HCl and five times with water, dried over $MgSO_4$, and evaporated in vacuo to give 7.3 g of brown solid. The solid was chromatographed as above to give 2.0 g (28%) of alcohol **75**.

Quenching of the enolate at −78 °C with D_2O showed that the formation of enolate was close to 97%. Excess MoOPH, inverse addition, or lower temperature (−44 °C) did not improve the yield. A model study with *d*-camphor gave 61% α-hydroxylation.

***trans*-6,7-Dihydro-6-[(methylsulfonyl)oxy]-7-(3,4,5-trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one, 76, and Sulfonate 77.** To a solution of the alcohol **75** (2.00 g, 5.59 mmol) and triethylamine (1.60 mL, 10.2 mmol, distilled over CaH_2) in 100 mL of dry methylene chloride at −10 °C under a nitrogen atmosphere was added dropwise methanesulfonyl chloride (0.649 mL, 8.38 mmol, distilled over CaH_2) in 10 mL of dry methylene chloride. After 30 min, the solution was washed with water, saturated $CuSO_4$ solution, passed through silica gel, and evaporated to give 2.5 g of a foam. Chromatography on the Waters HPLC (6% ethyl acetate in methylene chloride, R_f 0.18) gave 1.1 g (45%) of sulfonate **77** and 1.4 g (55%) of mesylate **76**.

Mesylate **76**: light yellow solid; mp 185–187 °C; 200 MHz ^1H NMR ($CDCl_3$) δ 7.162 (1 H, s), 6.657 (1 H, s), 6.402 (2 H, s), 6.127 (1 H, d, J = 1.0 Hz), 6.109 (1 H, d, J = 1.0 Hz), 5.171 (1 H, d, J = 4.5 Hz), 4.400 (1 H, d, J = 4.5 Hz), 3.861 (3 H, s), 3.823 (6 H, s), 3.299 (3 H, s); IR (neat) 1715 (s), 1355 (bs), 1180 (s) cm^{-1}; mass spectrum (70 eV), m/e 436 (M^+, 38), 342 (12), 341 (26), 340 ($M^+ - CH_3OSO_2$, 100), 325 (11), 78 (4); high-resolution mass spectrum (70 eV), m/e 436.0843, calcd for $C_{20}H_{20}O_9S$ 436.0828.

Sulfonate **77**: 200 MHz ^1H NMR ($CDCl_3$) δ 7.017 (1 H, s), 6.616 (1 H, d, J = 2.6 Hz), 6.571 (1 H, s), 6.450 (2 H, s), 6.094 (1 H, d, J = 1.1 Hz), 6.065 (1 H, d, J = 1.1 Hz), 5.462 (1 H, dd, J = 6.6, 2.6 Hz), 4.235 (1 H, d, J = 6.6 Hz), 3.872 (3 H, s), 3.844 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 153.95 (s), 153.78 (s), 152.68 (s), 149.22 (s), 143.19 (s), 138.22 (s), 133.63 (s), 123.66 (s), 111.27 (d), 106.86 (d), 105.46 (d), 103.87 (d), 102.48 (t), 90.64 (d), 60.89 (q), 56.36 (q), 54.81 (d); IR (neat) 3050 (m), 1640 (w–m) cm^{-1}; mass spectrum (70 eV), m/e 418 (M^+, 100), 354 ($M^+ - SO_2$, 23), 327 (20), 326 (99), 325 (80), 311 (70), 139 (16); high-resolution mass spectrum (70 eV), m/e 418.0760, calcd for $C_{20}H_{18}O_8S$ 418.0722.

The yield of sulfonate **77** could be reduced by using less triethylamine.

6,7-Dihydro-6β-[(methylsulfonyl)oxy]-5α-methyl-7α-(3,4,5-trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxol-5β-ol, 78, and 7-(3,4,5-Trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxole-5,6-dione, 79. To a solution of the mesylate **76** (1.4 g, 3.21 mmol) in 150 mL of dry THF at −78 °C under a nitrogen atmosphere was added methyllithium (2.7 mL of a 1.3 M solution, 3.53 mmol) in ether. ^1H NMR analysis of an aliquot after 1 h showed 50% conversion to **78** and **79** (1:1). After 2 h, the solution was warmed to 25 °C for 1 h. The THF was removed and methylene chloride was added. The organic phase was washed with water and 5% Na_2CO_3, dried over $MgSO_4$, and evaporated in vacuo to give 1.5 g of a yellow solid. The solid was chromatographed on a Waters HPLC (18% ethyl acetate in methylene chloride, R_f 0.13) to give 0.6 g (41%) of the mesylate **78** and a small amount (18% NMR yield) of dione **79**.

Mesylate **78**: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.906 (1 H, s), 6.461 (2 H, s), 6.411 (1 H, s), 5.985 (1 H, d, J = 1.1 Hz), 5.948 (1 H, d, J = 1.1 Hz), 4.838 (1 H, d, J = 7.9 Hz), 4.461 (1 H, d, J = 7.9 Hz), 3.857 (3 H, s), 3.830 (6 H, s), 2.610 (3 H, s), 1.699 (3 H, s); IR (neat) 3400 (bs) cm^{-1}; mass spectrum (70 eV), m/e 435 (M^+ – OH, 12), 434 (M^+ – H_2O, 52), 356 (M^+ – $MeSO_3H$, 38), 355 (M^+ – $MeSO_3H$ – H, 100), 354 (16), 338 (M^+ – H_2O – $MeSO_3H$, 25), 327 (64), 313 (19), 312 (53), 297 (38), 296 (63), 295 (11), 187 (12), 159 (21), 113 (11), 96 (37), 81 (14), 79 (43), 71 (10), 65 (29); high-resolution mass spectrum, m/e 434.1077, calcd for $C_{21}H_{22}O_8S$ 434.1036.

No ring contraction was observed even when the solution was allowed to stir for 3 days or HMPA was added.

Dione **79**: yellow solid: mp 224–226 °C dec; 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.349 (1 H, s), 6.820 (1 H, s), 6.259 (2 H, s), 6.183 (1 H, d, J = 0.8 Hz), 6.170 (1 H, d, J = 0.8 Hz), 4.541 (1 H, s), 3.823 (3 H, s), 3.796 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 192.19, 185.35, 156.54, 153.91, 149.46, 149.06, 133.43, 132.58, 106.81, 106.10, 103.41, 102.91, 60.92, 56.37, 52.37; IR (neat) 1750 (m), 1700 (s) cm^{-1}; mass spectrum (70eV), m/e 356 (M^+, 41), 328 (M^+ – CO, 47), 313 (30), 298 (21), 297 (100), 253 (16), 84 (17), 63 (17).

***trans*-6,7-Dihydro-6-[(*p*-tolylsulfonyl)oxy]-7-(3,4,5-trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one and Dione 79.** A solution of the alcohol **75** (85 mg, 0.237 mmol) in 8 mL of dry THF was cooled to –78 °C under a nitrogen atmosphere and *n*-butyllithium (172 mL of 1.52 M solution, 0.261 mmol) in hexane was added. After 1 h at –78 °C, a solution of recrystallized *p*-toluenesulfonyl chloride (50 mg, 0.261 mmol) was added. After 0.5 h at –78 °C, the solution was warmed to 25 °C for 1 h. Methylene chloride was added and the solution washed with 5% $NaHCO_3$, dried over $MgSO_4$ and evaporated in vacuo to give 102 mg of a yellow solid. ^{1}H NMR analysis showed the presence of 41% of the tosylate and 20% dione **79**. The two compounds could be separated on preparative TLC (6:1 methylene chloride–ethyl acetate): tosylate R_f 0.48, dione **79** R_f 0.40.

Tosylate: white solid, mp 216–218 °C dec; 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.681 (2 H, d, J = 8.5 Hz), 7.225 (2 H, d, J = 8.5 Hz), 7.123 (1 H, s), 6.549 (1 H, s), 6.259 (2 H, s), 6.093 (1 H, d, J = 1.0 Hz), 6.076 (1 H, d, J = 1.0 Hz), 5.077 (1 H, d, J = 4.5 Hz), 4.314 (1 H, d, J = 4.5 Hz), 3.870 (3 H, s), 3.796 (6 H, s), 2.425 (3 H, s); IR (neat) 1715 (s) cm^{-1}.

5-Methyl-7-(3,4,5-trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-ol, 81. To a solution of the mesylate **78** (73 mg, 0.162 mmol) in 4 mL of dry THF under a nitrogen atmosphere at 25 °C was added a solution of potassium *tert*-butoxide (24 mg, 0.214 mmol) in 1 mL of dry THF. After 30 min, methylene chloride and water were added. The organic phase was washed with water, dried over $MgSO_4$, and evaporated in vacuo to give 59 mg (100%) of pure alcohol **81** as an oil which is unstable. Use of potassium hydride gave a lower yield of **81**: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.989 (1 H, s), 6.879 (1 H, s), 6.714 (1 H, s), 6.227 (1 H, s), 5.960 (1 H, s), 3.890 (9 H, s), 1.622 (3 H, s); IR (neat) 3400 (bs), 2900 (s), 1570 (s), 1460 (s), 1410 (s), 1345 (s), 1230 (s), 1120 (s), 1030 (s) cm^{-1}.

7-(3,4,5-Trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxole-5,6-dione 6-Oxime, 82. When the procedure of Cava[38] was modified, a solution of concentrated HCl (29.2 mL, 351 mmol) in 100 mL of ethanol was mixed with a cold solution of the indanone **74** (15.0 g, 43.9 mmol) in 300 mL of methylene chloride and 500 mL of ethanol. Isoamyl nitrite (8.80 mL, 65.8 mmol) was added dropwise at 0 °C. The solution was allowed to warm to 25 °C and stir overnight to give a heavy white precipitate. The majority (70%) of the solvent was removed and water was added to precipitate the product. The precipitate was collected and dissolved in 370 mL of 1 N KOH and 1 L of H_2O. The aqueous phase was washed with ether and neutralized at 0 °C with cold diluted HCl. The precipitate was collected and dried under vacuum to give 15.5 g (95%) of oxime **82** as a light yellow solid: mp 222–227 °C; 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.280 (1 H, s), 6.688 (1 H, s), 6.338 (2 H, s), 6.100 (1 H, s), 6.084 (1 H, s), 5.004 (1 H, bs), 3.820 (3 H, s), 3.792 (6 H, s); IR (KBr) 3450 (s), 1705 (m) cm^{-1}.

6-Diazo-7-(3,4,5-trimethoxyphenyl)-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one, 83. When the procedure of Cava[38] was modified, to a mechanically stirred solution of pulverized oxime **82** (13.0 g, 35.1 mmol) in 370 mL (296 mmol) of 1 N KOH and 10.8 mL (161 mmol) of concentrated ammonium hydroxide at 0 °C in the dark was added dropwise 136 mL (91.3 mmol) of bleach (5% NaOCl). After stirring at 0 °C for 2 h, the mixture containing a yellow suspension was warmed to 25 °C and stirred for a further 9 h. The precipitate was collected, washed with water, dried, and chromatographed on a Waters HPLC (2 columns, 6% ethyl acetate in methylene chloride) to give 9.3 g (72%) of **83** as a yellow solid. An analytical sample was prepared by recrystallization from methylene chloride–ether to give yellow crystals: mp 185–195 °C dec; 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.211 (1 H, s), 6.641 (1 H, s), 6.390 (2 H, s), 6.060 (1 H, s), 6.053 (1 H, s), 5.146 (1 H, s), 3.840 (3 H, s), 3.822 (6 H, s); IR (neat) 2075 (s), 1660 (s) cm^{-1}; UV (MeOH) λ_{max} 344 (18 000), 314 (8800), 270 (9200), 231 (24 000) nm; λ 360 (4800), 400 (552) nm; UV (dioxane) λ_{max} 340 (17 000), 314 (9900), 274 (12 000), 232 (35 000) nm; mass spectrum (70 eV), m/e 368 (M^+, 25), 342 (34), 341 (21), 340 (M^+ – N_2, 100), 325 (88), 297 (33), 282 (23), 267 (25), 211 (32); high-resolution mass spectrum (70 eV), m/e 368.1002, calcd for $C_{19}H_{16}N_2O_6$ 368.1008. Anal. Calcd for $C_{19}H_{16}N_2O_6$: C, 61.96; H, 4.35. Found: C, 61.97; H, 4.37.

Methyl *trans*-5,6-Dihydro-6-(3,4,5-trimethoxyphenyl)-cyclobuta(*f*)-1,3-benzodioxole-5-carboxylate, 84, and 6,7-Dihydro-6-methoxy-7-(3,4,5-trimethoxyphenyl)-5*H*-indeno-[5,6-*d*]-1,3-dioxol-5-one, 85. A solution of the diazo ketone **83** (82 mg, 0.22 mmol) in 40 mL of methanol (freshly distilled from sodium) was deoxygenated by bubbling nitrogen through for 15 min and photolyzed in a Rayonet reactor (350 nm) for 5 h. The resulting yellow solution was evaporated and chromatographed on preparative TLC (SiO_2, 3:2 hexane–ethyl acetate) to give the following compounds in the order of elution.

(1) Benzocyclobutene **84**: 6 mg (7%); 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.791 (1 H, s), 6.730 (1 H, s), 6.498 (2 H, s), 5.961 (1 H, d, J = 1.5 Hz), 5.920 (1 H, d, J = 1.5 Hz), 4.672 (1 H, d, J = 2.2 Hz), 3.915 (1 H, d, J = 2.2 Hz), 3.832 (3 H, s), 3.826 (6 H, s), 3.782 (3 H, s); IR (neat) 1730 (s) cm^{-1}; UV (MeOH) λ_{max} 297 (6688) nm, tailing extended into 400 nm, λ 350 (500), 360 (380) nm; mass spectrum (70 eV, 110 °C), m/e 372 (M^+, 3), 313 (M^+ – CO_2Me, 10), 149 (39), 86 (76), 84 (100), 57 (24); high-resolution mass spectrum (70 eV), m/e 372.1207, calcd for $C_{20}H_{20}O_7$ 372.1209. When **84** was subjected to the same photolytic conditions, it decomposed completely within 4 h. When **84** was refluxed in $CDCl_3$ (passed through basic alumina) for 10 h, 42% decomposition was observed by ^{1}H NMR.

(2) Indanone **74**: 6 mg (8%).

(3) Ether **85**: 14 mg (17%); 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.179 (1 H, s), 6.686 (1 H, s), 6.225 (2 H, s), 6.071, 6.065, 6.054, 6.049 (2 H, ABq, J = 1.3 Hz), 4.590 (1 H, d, J = 7.0 Hz), 4.316 (1 H, d, J = 7.0 Hz), 3.817 (3 H, s), 3.772 (6 H, s), 3.389 (3 H, s); IR (neat) 1710 (s) cm^{-1}; mass spectrum (70 eV), m/e 372 (M^+, 21), 342 (17), 86 (65), 84 (100), 69 (18), 57 (22), 56 (28), 49 (44); high-resolution mass spectrum (70 eV), m/e 372.1216, calcd for $C_{20}H_{20}O_7$ 372.1209.

(4) An unknown compound: 9 mg (11%); 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.340 (1 H, s), 6.920 (1 H, s), 6.748 (1 H, s), 6.708 (2 H, s), 6.598 (2 H, s), 6.500 (1 H, s), 6.034 (1 H, s), 6.025 (1 H, s), 5.848 (1 H, s), 5.837 (1 H, s), 4.529 (1 H, d, J = 4.7 Hz), 4.400 (1 H, d, J = 4.7 Hz), 4.210 (1 H, s), 3.845 (3 H, s), 3.774 (6 H, s), 3.760 (3 H, s), 3.707 (6 H, s), 3.655 (3 H, s); IR (neat) 1735 (s), 1690 (s) cm^{-1}; mass spectrum (70 eV), m/e 712 (M^+, 96), 653 (M^+ – CO_2Me, 6), 372 (benzocyclobutene **84**$^+$, 25), 340 (27), 313 (100), 282 (27), 55 (46); high-resolution mass spectrum (70 eV), m/e 712.2143, calcd for $C_{39}H_{36}O_{13}$ 712.2156. This compound is probably the γ-keto ester formed by insertion of the α-keto carbene from **83** into the CH bond α to the ester of **84**.

The photolysis was also run under different conditions. **(A) Solvent.** (1) When dioxane–water (5:1) was used as the solvent with 2 equiv of $NaHCO_3$, 0.8% of the acid corresponding to **84** was obtained, which decomposed completely after 3 h in refluxing $CDCl_3$. (2) When methanol/benzene or methanol containing 59 equiv of NaOMe was used as the solvent, no change in the yield of **84** was observed. (3) When *tert*-butyl alcohol was used as the solvent, approximately 1% yield of the *tert*-butyl ester corresponding to **84** was observed. (4) When cyclohexylamine was used as the solvent, the cyclohexyl amide corresponding to **84** was obtained in 7% yield: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.821 (1 H, s), 6.781 (1 H, s), 6.437 (2 H, s), 6.021 (1 H, d, J = 1.3 Hz), 5.954 (1 H, d, J = 1.3 Hz), 4.865 (1 H, d, J = 5.7 Hz), 4.390 (1 H, d, J = 5.7 Hz), 3.809 (6 H, s), 3.783 (3 H, s), 1.700–0.900 (11 H, m).

(B) Temperature. Lowering the temperature to −23 or −78 °C gave poorer yields of **84**, despite decreased formation of **74** and **85**.

(C) Light Source. (1) When a Corning 0-52 filter (cutoff at 345 nm) was used, a lower yield of **84** was obtained. (2) When 4,4′-bis(dimethylamino)benzophenone (104 h of photolysis) or benzophenone (16 h of photolysis) was used as sensitizer together with a Corning 0-52 filter, a lower yield of **84** was obtained.

Diazirene 86. When a Corning 3-74 filter (cutoff at 406 nm) was used and the photolysis carried out for 88 h at 0 °C, 60% of the diazirene **86** was isolated: mp 147–160 °C dec; 200 MHz ^{1}H NMR ($CDCl_3$) δ 7.223 (1 H, s), 6.740 (1 H, s), 6.245 (2 H, s), 6.116 (2 H, s), 4.014 (1 H, s), 3.830 (3 H, s), 3.803 (6 H, s); IR (neat) 1700 (s) cm^{-1}; mass spectrum (70 eV), *m/e* 368 (M^+, 95), 340 ($M^+ - N_2$, 64), 325 (100), 297 (31), 267 (25), 211 (24). Anal. Calcd for $C_{19}H_{16}N_2O_6$: C, 61.96; H, 4.35. Found: C, 62.08; H, 4.34.

***trans*-5,6-Dihydro-6-(3,4,5-trimethoxyphenyl)cyclobuta(*f*)-1,3-benzodioxolecarboxylic Acid, 87.** A solution of benzocyclobutene **84** (1.50 g, 4.04 mmol), 20 mL of 1 N KOH in 30 mL of methanol, and 75 mL of THF was kept at 0 °C for 2 days. Water and methylene chloride were added. The aqueous phase was acidified and extracted with methylene chloride. The organic phase was washed with water, dried over $CaSO_4$, and evaporated in vacuo to give 1.00 g (69%) of the acid **87** as a foam. The compound showed 30% decomposition when left at 25 °C overnight: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.810 (1 H, s), 6.747 (1 H, s), 6.501 (2 H, s), 5.973 (1 H, d, *J* = 1.35 Hz), 5.929 (1 H, d, *J* = 1.35 Hz), 4.701 (1 H, d, *J* = 1.75 Hz), 3.955 (1 H, d, *J* = 1.75 Hz), 3.836 (3 H, s), 3.827 (6 H, s); IR (neat) 3200–2500 (bm), 2900 (s), 1700 (s), 1590 (s), 1450 (s), 1420 (s), 1140 (s), 1230 (s), 1125 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_7$: C, 63.69; H, 5.03. Found: C, 63.95; H, 4.79.

Attempted Preparation of Methyl Ketone 88. Several reactions were tried in an attempt to make methyl ketone **88** but all resulted in mixtures of products. At best, there was ~10% (NMR) of a product having absorption at δ 4.60 (1 H, d) for a benzocyclobutene proton α to a ketone and at δ 2.29 (3 H, s) for an acetyl methyl group. The IR showed a strong ketone band at 1710 cm^{-1}.

Condition A. Acid **87** in THF was treated with 2.0, 2.5, or 3.0 equiv of methyllithium for a few hours at room temperature.

Condition B. The sodium salt of acid **87** in THF was treated with 1 or 2 equiv of thionyl chloride and added to 3 or 4 equiv of lithium dimethylcuprate. IR analysis of the first step showed no acid chloride formation. ^{1}H NMR analysis of the first step showed that the benzocyclobutene ring had opened to a large extent.

(*E*)-3-Carbomethoxy-2-propenyl *trans*-6-(3,4,5-Trimethoxyphenyl)cyclobuta(*f*)-1,3-benzodioxole-5-carboxylate, 90. To a solution of methyl 4-hydroxy-2-butenoate (**5**) (133 mg, 1.15 mmol) in 2 mL of dry THF under a nitrogen atmosphere at 0 °C was added a cold solution of dicyclohexylcarbodiimide (179 mg, 0.87 mmol) in 3 mL of dry THF. The acid **87** (82 mg, 0.23 mmol, ~73% pure by ^{1}H NMR) in 2 mL of dry THF was added slowly at 0 °C. After 15 min, the colorless solution turned turbid red. The mixture was allowed to stir at 0 °C for 4 h. TLC analysis showed that the reaction was over in an hour. The solid (*N,N*′-dicyclohexylurea) was filtered off and the THF was evaporated. Methylene chloride was added to dissolve the product. Any precipitate left was filtered off. The organic phase was washed once each with water and brine and evaporated in vacuo to give 275 mg of a brown solid. A small amount of $CDCl_3$ was added and any undissolved solid was again filtered off. Preparative TLC (2 × 2 mm silica gel, 35% ethyl acetate in benzene R_f 0.5) was performed to give 46 mg of a yellow solid which contained 37% by weight (^{1}H NMR) of *N,N*′-dicyclohexylurea and 63% by weight (^{1}H NMR) of the desired ester **90**. The yield of ester **90** is 23% [38% if the purity (73%) of the starting material **87** is taken into account]: 200 MHz ^{1}H NMR ($CDCl_3$) δ 6.99 (1 H, td, *J* = 15.5, 5.2 Hz), 6.79 (1 H, s), 6.63 (1 H, s), 6.47 (2 H, s), 5.96 (1 H, d, *J* = 1.4 Hz), 5.90 (1 H, d, *J* = 1.4 Hz), 4.90–4.80 (1 H, m), 4.55 (1 H, d, *J* = 2.0 Hz), 4.13 (1 H, d, *J* = 2.0 Hz), 3.83 (3 H, s), 3.82 (6 H, s), 3.75 (3 H, s), 2.30–0.80 (urea, m); IR (neat) 3300 (urea, w), 1695 (s), 1645 (urea, s) cm^{-1}; mass spectrum (70 eV), *m/e* 456 (M^+, 42), 358 (17), 288 (15), 283 (17), 82 (100, cyclohexene from urea); mass spectrum (16 eV), *m/e* 456 (M^+, 100), 224 (urea, 4), 82 (34).

4-Carbomethoxy-5-(3,4,5-trimethoxyphenyl)-3aα,4β,5β,10bβ-tetrahydrofuro[3′,4′:5,6]naphtho[2,3-*d*][1,3]-dioxol-1(3*H*)-one, 92, and 3aβ,4α,5β,10bβ-Tetrahydro Isomer 93. A solution of the ester **90** (9.6 mg, 0.021 mmol) and 6.4 mg (0.029 mmol) of *N,N*′-dicyclohexylurea (as an inseparable contamination) in 5 mL of dry toluene (distilled over sodium) was bubbled with nitrogen for 10 min and refluxed for 3.5 h. After cooling and evaporation of the solvent, the product was chromatographed on preparative TLC (0.5 mm silica gel, 40% ethyl acetate in benzene, R_f = 0.27) to give 2.1 mg (22%) of a white solid consisting of a 3:1 mixture of the two isomeric lactones **92** and **93**. Substitution of benzene for toluene gave the same yield and diastereomeric ratio. The major isomer **92** could be enriched to 93% purity (7% **93**) by repetitive (three times) elution on preparative TLC (0.5 mm silica gel, 25% ethyl acetate in benzene) and isolating the lower portion of the band.

The 200-MHz ^{1}H NMR spectra of pure **92** and pure **93** could be obtained by using the dual display program of the Bruker WP200 spectrometer to normalize and to subtract two spectra consisting of different ratios of isomers. The chemical shifts and coupling constants were assigned by a complete proton–proton decoupling experiment on the mixture: for 200-MHz ^{1}H NMR spectra, see Table I; IR (neat) (3:1 mixture of **92** and **93**) 2850 (s), 1775 (s), 1730 (s), 1590 (s), 1500 (s), 1480 (s), 1460 (s), 1425 (m), 1330 (m), 1240 (s), 1220 (s), 1175 (m), 1150 (m), 1120 (s), 1035 (m), 730 (m) cm^{-1}; mass spectrum (70 eV), *m/e* 456 (M^+, 100), 441 ($M^+ - CH_3$, 3), 425 ($M^+ - CH_3O$, 6), 397 ($M^+ - CO_2CH_3$, 6), 396 ($M^+ - HCO_2CH_3$, 11), 288 (30), 229 (12), 185 (17), 181 (10), 168 (11); high-resolution mass spectrum (70 eV), *m/e* 456.1410, calcd for $C_{24}H_{24}O_9$ 456.1418.

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Registry No. **5**, 29576-13-4; **15**, 15930-53-7; **16**, 7748-58-5; **17**, 56251-58-2; **1m**·HCl, 94670-72-1; **18**, 94670-74-3; **19a**, 94670-75-4; **19b**, 94670-76-5; **20a**, 94670-77-6; **20b**, 94706-16-8; (±)-**21**, 94670-78-7; (±)-**23**, 94670-79-8; (±)-**26**, 94670-80-1; **27**, 27452-03-5; (±)-**28**, 89023-87-0; (±)-**29**, 94670-81-2; (±)-**30**, 94670-82-3; **31**, 94670-83-4; **32**, 2675-79-8; **34**, 91-10-1; (±)-**35**, 94670-84-5; (±)-**36a**, 94670-85-6; (±)-**36b**, 94670-86-7; **37**, 7115-91-5; **41**, 1449-46-3; **42E**, 94670-88-9; **42Z**, 94670-87-8; (±)-**43**, 94706-17-9; (±)-**44**, 94670-89-0; **45**, 40804-81-7; (±)-**46**, 94670-90-3; **47**, 94670-91-4; **48**, 52806-34-5; **49**, 94670-92-5; (±)-**50**, 94670-93-6; **51**, 94670-94-7; (±)-**52**, 94670-95-8; (±)-**53**, 94670-96-9; **56**, 42123-15-9; (±)-**57**, 94670-97-0; (*E*)-**58**, 94670-98-1; (*Z*)-**58**, 94670-99-2; **61**, 94671-00-8; **62a**, 94671-01-9; **63**, 94671-02-0; **64**, 74879-22-4; **65**, 86-81-7; **66**, 75101-84-7; **66** (mesylate), 94671-03-1; **66** (methyl ether), 94671-04-2; **68**, 94671-05-3; **69**, 94671-06-4; **70**, 3162-29-6; **71**, 54011-33-5; **72**, 94671-07-5; **73**, 94671-08-6; (±)-**71**, 94671-09-7; (±)-**74** (trimethylsilyl enol ether), 94671-10-0; (±)-**75**, 94671-11-1; (±)-**75** (tosylate), 94671-12-2; (±)-**76**, 94706-18-0; (±)-**77**, 94671-13-3; (±)-**78**, 94671-14-4; (±)-**79**, 94671-15-5; (±)-**81**, 94671-16-6; (±)-**82**, 94671-17-7; (±)-**83**, 94671-18-8; (±)-**84**, 94706-19-1; (±)-**84** (cyclohexylamide), 94671-19-9; **85**, 94671-20-2; (±)-**86**, 94671-21-3; (±)-**87**, 94671-22-4; (±)-**90**, 94671-23-5; (±)-**92**, 94671-24-6; (±)-**93**, 94730-94-6; CH_2=CHOAc, 108-05-4; $NCCH_2CO_2H$, 372-09-8; furan, 110-00-9; cyclopentadiene, 542-92-7; 6-aminobenzo-1,3-dioxole-5-carboxylic acid, 20332-16-5; 3-(6-bromobenzo-1,3-dioxol-5-yl)-2-cyanopropenoic acid pyridine salt, 94671-26-8; 4-bromo-2,6-dimethoxyphenol, 70654-71-6.