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 intermediate of the o-quinodimethane 91 which cyclizes from the endo transition state 91 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 9 may prove successful. Several possible approaches to the synthesis of the trans-2-aryldihydrobenzocyclobutenol 4 are described. The benznyl 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-iodanode 74 prepared in good yield from piperonal 14. The diol monomethylate 78, prepared from 74, suffered base-catalyzed E2 elimination rather than the desired rearrangement to 80. The diazo ketone 85 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 ketone 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 1H NMR and analogy to the spectra of similar compounds in the literature.

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**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. 4

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

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The results of extensive phase I clinical testing produced two drugs, designated VM-26 (for 4'-demethyl-1-O-[4,8-O- (2-thienylmethylene) -β- d-glucopyranosyl] 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 therapeutic
benefit against Hodgkin’s disease. Further testing has shown these compounds to be effective in cancer chemotherapy either alone or in combination with other antineoplastic agents.

The active drugs 2 and 3 were prepared by Kuhn and von Wartburg from podophyllotoxin 1 via several steps in relatively good overall yield. Three syntheses of podophyllotoxin 1 have been reported. The original synthesis of Gensler and Gatsonis 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 and Kende 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. This compound would be prepared from the carvedilol, via 3, 4, and 5. 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) 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 9s. If the Alder endo transition state rules hold for this cycloaddition, namely if the endo transition state
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 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-arylido-hydrobenzocyclobutene 4. Although many synthetic approaches have been attempted, we have yet to prepare this compound. However, we have synthesized its analogue 8' (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. 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 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)benzene 11 might react with a 2-alkoxy-3,4,5-trimethoxystyrene 12 to produce the desired cycloadduct 13. The benzene 11 had not been reported previously in the literature but could be prepared in relatively straightforward fashion from piperonal 14. The known 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 tetrfluoroborate 18 in good yield. One potential precursor of the desired benzene 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 benzene 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 benzene 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-3-pyrrolidinostyrene, 4,5-allene, ethyl vinyl ether, methyl acrylate, etc.

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 benzene 11. Diazotization of this known amino acid, 4,5-(methylenedioxy)-2-aminobenzoic acid, with isomyl 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 isomyl nitrite in refluxing vinyl acetate as solvent. Thus to date all attempts to utilize the benzene 11 in a [2 + 2] cycloaddition approach to molecules related to 4 have failed.

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

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halohydrins of this sort are well-known and have been carried out on the halohydrins themselves or on their salts. 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 CrO₂ oxidation of the 1-bromodi-hydrobenzocyclobutene or bromination of the benzocyclobutene. 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 prevented us from carrying out this reaction on a large scale. For this reason, we decided to prepare the necessary benzocyclobutene 31 by an application of the Kametani procedure.

Treatment of bromopiperonal 15 with cyanoacetic acid in pyridine afforded the Knoevenagel product which was reduced with borohydride to give the cyanocinnamic acid in 71% 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 was used to convert 28 into 31, namely thiophenolysis 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 and could be prepared from 3,4,5-tribromo-2,6-dimethoxyphenol (33) by reduction and methylation or from 2,6-dimethoxyphenol (34) by selective bromination and methylation. Preparation of the Grignard reagent 22a or the organolithium 22b to the bromo benzocyclobutene 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 benzocyclobutene related to 24 to find conditions under which the alchoholate was stable to ring opening. The known 2-bromobenzocyclobutene 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 alcohol 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 cyclobutene.28 The trans stereochemistry of the alcohol...
Synthesis of Podophyllotoxin

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 \(-78 \, ^\circ \text{C}\) 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 \(-78 \, ^\circ \text{C}\) but only upon warming to \(-35 \, ^\circ \text{C}\) 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)phenylmethyl anion, a process we have observed in other cases (vide infra). For example, treatment of 44 with sodium hydroxide in Me$_2$SO-$d_6$ 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 \(-98 \, ^\circ \text{C}\), to try to effect lithium-halogen exchange and cyclization, followed by the addition of tert-butyldimethylsilyl chloride at \(-98 \, ^\circ \text{C}\) 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 \(-78 \, ^\circ \text{C}\) 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 benzophone 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 dimethylsulfoxonium methylide gave a 97%
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-butylidemethylsilyl 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 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 benzocyclobutenes observed.

Other Cyclization Routes. We also attempted to assemble the benzocyclobutenes system by preparing an ortho-disubstituted piperonal 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 most direct route to 59 involved condensation of the diion 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 (D₂O) gave the expected deuterated product 62a in 74% yield with a small contamination by the monodeutero product 62b, in which the deuteration was located nearly exclusively at the dithiane carbon. This would imply that lithium-halogen exchange occurs initially to give the aryllithium which then undergoes two competing deprotonations, one by tert-butyllithium to give the diion 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 D₂O 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 aryllithium 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 diisopropylamine at -78 °C for 2 h and then 25 °C for 3 h followed by quenching with D₂O. However, the expected monodeutero 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 intermediary of the benzene 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 38% alcohol 66 in 77% yield. All attempts to convert the alcohol into a leaving group such as bromide, chloride, or mesylate to give

Synthesis of Podophyllotoxin

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 cat-ionic species at the aldehyde carbon. An authentic sample of the methoxylaldehyde 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 such as cyclobutanones and even trans-fused bicyclo-[4.1.0]heptan-2-one; (2) a Wolff rearrangement of a 2-diazo-1-indanone, a reaction preceded in this system. Thus we investigated the construction of 3-aryl indanones such as 74.

(a) Glycol Monosulfonate Rearrangement. Piperonal 14 was converted into the known 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 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 or peracid oxidation of the trimethylsilyl enol ether. We assigned the structure as trans for two reasons given in the text.

period of time, a 1:1 mixture of the cyclopentanone carbonyl and the S-methyl group. Presumably the system prefers to lose the mesylate group. Presumably the system prefers to lose the

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 2-cyclopenten-1-one are 2.2 Hz for the trans and 7.2 Hz for the cis. (2) The 200-MHz 1H NMR of 75 showed a coupling of 4.3 Hz for these two protons, more indicative of a trans relationship than a cis one. 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 1H and 13C 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 methylthiolium 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 methanesulfonic 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 3-elimination rather than undergo rearrangement to the strained dihydrobenzocyclobutene system 80. No other reaction conditions could be found to rearrange 78 into 80.

(b) Wolff Rearrangement. The final route to the benzocyclobutenes 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. 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

Scheme XI

Scheme XII

(37) For example, the coupling constants for the protons at C4 and C5 of 2-cyclospen-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 78 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.

promoted coupling of the acid carried out to give the ester to the acid chloride with thionyl chloride followed by verturation to give the acetate out a Baeyer-Villiger oxidation with retention of configuration. Therefore it is very likely that synthetic approach to the epipodophyllotoxins, we decided the ester in. However, the two attempts at converting amounts of material were available. Hydrolysis of the ester constant of the cyclobutane protons which was observed (based on the observed Blomquist and Bottomley2 reported in similar compounds 84 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 Bottomley2 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 hence the alcohol 4. However, the two attempts at converting 87 into 88 failed: (1) treatment with 2 equiv of methylthionium; (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 a toluene solution of 90 for 3.5 h followed by preparative TLC afforded in 2:1:1 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 91xn 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 stereochimetry 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

| Table 1. Chemical Shifts, Multiplicities, and Coupling Constants for Pentacyclic Lactones 92 and 93 |
|---|---|---|---|
| 92 | 93 |
| Proton | Multiplicity | δ | Multiplicity |
| 5 | 7.132 ppm | s | 7.018 ppm | s |
| 8 | 6.485 | s | 6.233 | s |
| 2' | 6.072 | s | 6.290 | s |
| 3' | 5.969 | s | 5.924 | ABq |
| OCH3 | 5.943 | s | 5.910 | ABq |
| 5.936 | s | 5.903 |
| 11'' | 4.468 | dd | 4.150 | d |
| 1 | 4.461 | d | 4.016 | d |
| 11 | 4.164 | d | 3.998 | 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 |
| CO2Me | 3.717 | s | 3.474 | s |
| 3 | 3.185 | ddd | 3.228 | ddd |
| 2 | 3.044 | d | 2.836 | d |

<table>
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<th>Coupling constants</th>
<th>92</th>
<th>93</th>
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<td>J1,2</td>
<td>4.6</td>
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<td>J2,3</td>
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</tr>
<tr>
<td>J3,4</td>
<td>7.8</td>
<td>7.5</td>
</tr>
<tr>
<td>J3,5</td>
<td>0</td>
<td>5.2</td>
</tr>
<tr>
<td>J3,11</td>
<td>5.3</td>
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</tr>
<tr>
<td>J11,11</td>
<td>10.1</td>
<td>9.9</td>
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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., 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 pseudoequatorial (e.g., podophyllotoxin, epi-podophyllotoxin), it causes H\textsubscript{2} and H\textsubscript{5} 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\textsubscript{2} and H\textsubscript{5}, do not lie in the shielding zone but more in the deshielding zone and thus are deshielded. The effect on H\textsubscript{4} is similar but in the opposite direction, namely H\textsubscript{4} lies above the plane of the E ring in conformation B and is thus shielded. 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 pseudoequatorial and is farther out of the plane of the B ring. Thus in conformational A one would expect H\textsubscript{1} to be at lower field, H\textsubscript{6} to be at lower field, and H\textsubscript{2,5} to be at higher field than the corresponding protons in conformation B. This is the case for all of the known podophyllotoxin derivatives. An examination of the chemical shifts of the protons of the major and minor isomers (Table I) show that in the major isomer H\textsubscript{1} and H\textsubscript{6} are at lower field and H\textsubscript{2,5} 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\textsubscript{1} and H\textsubscript{2} (J\textsubscript{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\textsubscript{1}-C-C-H\textsubscript{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 9 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 (1H NMR) were taken on a Varian T-60 or Bruker WP-200 spectrometer and are so indicated. Carbon NMR spectra (13C NMR) were taken 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 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, namely, by using bromine in acetic acid, but with the variation of adding a little bit of lead acetate in carbon disulfide to the reaction mixture. In this manner a 60–70% yield of the crude bromide could be obtained, which could be recrystallized from ethanol to give pure 15: mp 127–129°C [lit.44 mp 126–127°C; 60 MHz 1H NMR (CDCl3) δ 10.15 (1 H, s), 7.35 (1 H, s), 7.13 (1 H, s), 6.10 (2 H, s), 5.85 (2 H, s)].

**5-Bromo-6-nitrobenzo-1,3-dioxole, 18.** Concentrated nitric acid (60 mL) with cooled to 0 °C with stirring was added to 3-(4-nitrophenyl) pyridine (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 18 as yellow needles: 60 MHz 1H NMR (CDCl3) δ 7.4 (1 H, s), 7.1 (1 H, s), 6.1 (2 H, s).

**Synthesis of Podophyllotoxin**

**5-Bromo-6-nitrobenzo-1,3-dioxole, 18.** 5-Bromo-6-nitrobenzo-1,3-dioxole (18) (1.7 g, 5.4 mmol) was dissolved in 10 mL of ethyl acetate and concentrated by rotary evaporation to afford 0.97 g (85%) of the salt.

**5-Amino-6-bromobenzo-1,3-dioxole Hydrochloride, 19a.** 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 at 5 min 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 C9H8O3BrF · HCl: C, 39.2; H, 1.26. Found: C, 39.26; H, 1.21.

**5-Bromo-6-fluorobenzol, 1,3-dioxole, 19a.** The diazonium tetrafluoroborate 18 (1.7 g, 5.4 mmol) was dissolved in 10 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 (Na2SO4) and concentration by rotary evaporation, afforded 0.137 g (69%) of 19a as an oily solid: 60 MHz 1H NMR (CDCl3) δ 6.95 (1H, d, J = 6 Hz), 6.7 (1H, d, J = 6 Hz), 6.0 (2H, 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 at 0 °C. After an additional 10 min at 0 °C the green solution was poured with good stirring into 10 mL of 0.1 M aqueous potassium iodide. The aqueous mixture was extracted with methylene chloride and the methylene chloride solution was washed with aqueous sodium bisulfite. Drying (Na2SO4) 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 1H NMR (CDCl3) δ 7.92 (1H, s), 7.7 (1H, s), 7.1 (1H, s), 5.95 (2H, s). Anal. Calcd for C9H8O3BrI: C, 39.2; H, 1.22. Found: C, 39.26; 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-iodobenz-1,3-dioxole (19b) (0.344 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, 1.08 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 (Na2SO4) and concentrated by rotary evaporation to afford 0.39 g of a red oil. Preparative thin-layer chromatography on silica gel (30% hexane in methylene chloride) afforded 20a (100 mg, 0.32 mmol) as a yellow solid: 200 MHz 1H NMR (CDCl3) δ 7.15 (2H, d, J = 1 Hz), 6.85 (2H, s), 5.9 (2H, m), 5.65 (2H, d, J = 1 Hz); mass spectrum, m/e 188 (M+).

**Using magnesium:** A solution of 5-bromo-6-iodo benz-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 (50 mg, 1.25 mmol), 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-iodo benz-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 heated under nitrogen for 24 h at 70 °C. 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 (Na2SO4) and concentrated by rotary evaporation to afford 0.21 g of a yellow oil. The crude product mixture was separated by...
to insure that it is still dry with the liquid.

A further

flask. A very small piece of potassium was added to ammonia

is stirred for a further

solution was poured onto water

pension of the cyano acid

at room temperature for

been added the reaction mixture was heated at


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 (55–60 °C, 100 mL) was cooled in an ice bath to 0 °C and sulfur chloride (32.4 g, 34 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, benzensulphenyl chloride, is a red liquid and should be stored under an argon atmosphere in the freezable state. The

A suspension of the pyridine salt (5.0 g, 29.6 mmol) in warm vinyl acetate (100 mL) was condensed and dried over potassium hydroxide (2 g, 35 mmol) 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 50–85 °C until the salt had dissolved. Sulfon chloride (1.40 g, 6.95 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 28 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 (38% of theoretical) mp: 170–171 °C (softens at 140 °C; 200 MHz 1H NMR (CDCl3) δ 7.022 (1 H, s), 6.688 (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 pyridine salt (2.0 g, 69.25 mmol) in benzene (25 mL) and methylacrylamide (0.5 mmol) 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 1H NMR (CDCl3) 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 (CHCl3) 2250 cm⁻¹. Anal. Calc'd for C8H7BrNO: C, 57.87; H, 4.02; N, 4.42. Found: C, 57.84; H, 3.98; N, 4.56.

5-Cyano-5,6-dihydrocyclobuta(f)-1,3-benzodioxole, 28. Ammonia (350 mL) was condensed and dried over potassium (~0.5 g) and the black oil persists and may be redissolved into a second reaction 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 which can vary. It may be necessary to add another crystal or two of ferric nitrate. The reaction mixture is stirred for a further 30 min after decolorization. The nitride 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 nitride. Once the reaction is complete it is quenched by careful addition of ammonium chloride (20 g) and the resulting ammonium product is stirred at ambient temperature for 1 h. The color of the reaction changes from yellow to orange during this time. The reaction mixture was poured onto ether (2 × 25 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 (Na2SO4). The dry etheral solution was filtered and concentrated under reduced pressure; the residue was a pale yellow solid which was purified by preparative thin-layer chromatography on silica gel as support and ether pentane ether (1:3) as eluent. The chromatogram gave two products, the less polar product (22 mg, 20% yield) being the desired ketone 31 and the more polar (60 mg, 45%) being the cyanohydrin 30. The cyanohydrin 30 (60 mg) was added to a solution of 2 g sodium hydroxide (2 mL) and aqueous acetone (25%) (2 mL) and stirred under nitrogen for 1 h. The color of the reaction changes from yellow to orange during this time. The reaction mixture was poured onto ether (2 × 25 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 (Na2SO4). The dry etheral solution was filtered and concentrated under reduced pressure; the residue was a pale yellow solid which was purified by preparative thin-layer chromatography on silica gel as support and ether pentane 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, 45%) being the cyanohydrin 30. The cyanohydrin 30 (60 mg) was added to a solution of 2 N sodium hydroxide (2 mL) and aqueous acetone (25%) (2 mL) and stirred under nitrogen for 1 h. The color of the reaction changes from yellow to deep red. The solution is poured onto ether (50 mL) and separated. The etheral 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 (Na2SO4). 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 1H NMR (CDCl3) δ 6.95 (1 H, s), 6.57 (1 H, s), 6.05 (2 H, s), 3.83 (2 H, s); IR (liquid film) 1770-1780 cm⁻¹.

6-Bromo-6H-cyclobuta[1,3]-benzodioxol-5-one, 23. The cyclobutene 31 (54 mg, 0.33 mmol) was dissolved in dry carbon tetrachloride (4 mL) and recrystallized from benzene-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 1H NMR (CDCl3) δ 7.040 (1 H, s), 6.790 (1 H, s), 6.132 (2 H, s), 6.520 (1 H, s); IR (liquid film) 1770–1780 cm⁻¹; mass spectrum, m/e (16 eV) 244, 242 (M⁺, 14%), 163 (M⁺ – 81, M⁺ – 79, 77%), 135 (M⁺ – 109, M⁺ – 107, 79%).

3,4,5-Trimethoxybromobenzene, 32, from the Phenol 34. When the literature procedure of Foley and co-workers (1986) 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 g (0.28 mol) of anhydrous MeOH (distilled over MeOna) in 1.5 L of anhydrous chloroform (distilled over CaH2) was treated with 188.7 g (1.06 mol) of N-bromosuccinimide at -45 to -35 °C to give, after workup, 145.6 g [65% (lit. 62% re-crystallized yield)] of white crystals, mp 158-159 °C. 200 MHz 1H NMR (CDCl3) 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, 79%).

Benzytriphenylphosphonium 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-phenylethyl)benzo-1,3-dioxole, 42( E/Z). 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-Butyl lithium (1.05 mmol) was then dripped into the cooled suspension. The 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 x 100 mL). The ethereal extracts were dried (Na2SO4), filtered, and concentrated to leave an oil which was a mixture of the Z isomer 42(Z) and the E isomer 42(E). The two isomers could be separated on the Waters 500 HPLC (after a short column filtration to remove Ph₃P=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 1H NMR (CDCl3) δ 7.15 (5 H, s), 7.00 (1 H, s), 6.80 (1 H, s), 6.50 (2 H, s), 5.80 (2 H, s).
42(E): 200 MHz 1H NMR (CDCl3) δ 7.80-6.85 (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 Ph₃P=O, which is a mixture of the two olefins 42(Z/E), 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 1H NMR. The reaction is complete when only one methyleneoxy peak at 5.95 is visible in the 1H NMR. The reaction was worked up by washing with solid sodium thiosulfate (2 x 50 mL) and dried (Na₂SO₄).

(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-Chloroperoxybenzoic acid (120 mg, 0.77 mmol) was added and the reaction mixture stirred for 2 h in dry dichloromethane (4 mL). The reaction mixture was filtered and concentrated to give 124 mg (84%) of the pure silyl ether as a colorless oil: 200 MHz 1H NMR (CDCl3) 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 (CDCl3) δ 1280 cm⁻¹.

Ethyl 2-(Bromomethyl)benzoate, 37. The bromo ketone 35 (100 mg, 0.55 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 (58%) of the benzate 37: 60 MHz 1H NMR (CDCl3) 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, 79%).
was subjected to preparative TLC on silica gel with benzene as eluent. A solution of 143.0 g (142 mmol) of 3-bromobenzyl alcohol 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 18 in 400 mL of dried THF was added at a relatively fast rate over a period of 30 min. After stirring at −78 °C, 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 MgSO₄ and evaporated in vacuo to give 56.9 g of solid. The desired 5,5-dimethyl-2-(4-(1,3-benzodioxol-5-yl)pentyl)cyclobutanol 44 was isolated by Waters 500 HPLC (SiO₂, 2 columns, hexane-ethyl acetate/hexane) to give 21.0 g (37%) of light yellow crystals: mp 137−140 °C; 200 MHz ¹H NMR (CDCl₃) δ 7.50 (2 H, m), 7.43 (1 H, s), 7.30 (2 H, s), 6.91 (1 H, s), 6.19 (2 H, s), 6.03 (1 H, bs), 5.94, 5.93, 5.920, 5.913 (2 H, Abq) J = 1.3 Hz, 3.80 (6 H, s), 3.796 (3 H, s), 3.029 (1 H, bs); IR (CDCl₃) 3400 (s) cm⁻¹. Anal. Calcd for C₂₀H₂₁O₆: C, 77.85; H, 6.72 (3 H, bs), 5.87 (2 H, bs), 4.17 (2 H, s); IR (neat) 1680 (s) cm⁻¹. 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 lithium bromide in ether. The solution turned turbid and was allowed to stir for 1.5 h. The reaction was quenched with three volumes of saturated ammonium chloride solution. Most of the THF was removed by evaporation 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 (CDCl₃) 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), 3.80 (6 H, s), 3.796 (3 H, s), 3.029 (1 H, bs), 1.54 (H, H, 2.5.2 Hz), 1.48 (2 H, bs). 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 lithium bromide in ether. The solution turned turbid and was allowed to stir for 1.5 h. The reaction was quenched with three volumes of saturated ammonium chloride solution. Most of the THF was removed by evaporation 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 (CDCl₃) 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), 3.80 (6 H, s), 3.796 (3 H, s), 3.029 (1 H, bs), 1.54 (2 H, bs). 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 lithium bromide in ether. The solution turned turbid and was allowed to stir for 1.5 h. The reaction was quenched with three volumes of saturated ammonium chloride solution. Most of the THF was removed by evaporation 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 (CDCl₃) 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), 3.80 (6 H, s), 3.796 (3 H, s), 3.029 (1 H, bs), 1.54 (2 H, bs). Attempts to improve the yield by inverse addition or use of a Grignard were not successful.
1H NMR (291 MHz, CDCl₃) δ 2.00 (3 H, s), 2.30 (2 H, s), 3.20 (3 H, s), 3.50 (2 H, m), 3.70 (2 H, s), 4.00-2.00 (4 H, m), 2.20-1.90 (4 H, m); mass spectrum (70 eV), m/e 344 (M⁺, 100), 329 (73), 301 (28), 298 (15), 157 (11), 149 (23), 135 (14), 75 (18).

Synthesis of Podophyllotoxin

1H NMR (291 MHz, CDCl₃) δ 10.162 (1 H, s), 3.82 (9 H, s); IR (neat) 2945 (m), 1630 (m), 1580 (s), 1490 (m), 1350 (m), 750 (s), 690 (m), 670 (w), 640 (w), 590 (m), 570 (w), 560 (m), 530 (w), 480 (w), 470 (w), 450 (w), 430 (w), 410 (w), 390 (w), 380 (s), 360 (w), 340 (w), 320 (w), 300 (s), 280 (w), 260 (w), 240 (w), 220 (w), 200 (w), 180 (w), 160 (w), 140 (w), 120 (w), 100 (w), 80 (w), 60 (w), 40 (w), 20 (w), 10 (w), 5 (w), 1 (w).
color changes to dark red over this time. The reaction was quenched by adding deuterium oxide to the reaction mixture and then stirring for 3 h at 0 °C. The aqueous phase was extracted with ether, and the potassium hydroxide solution was added. After cooling, the excess potassium hydroxide was neutralized with dilute acid. The solution was acidified with dilute hydrochloric acid. The white precipitate was washed with ether, filtered, and dried to give 3.4 g (77%) of 66 as pale yellow crystals: mp 123-125 °C.

The mesylate solution was transferred via a double-ended needle to a mixture of lithium bromide (289 mg, 3.09 mmol, oven dried) in 4 mL of HMPA (distilled over CaH₂) and 1 mL of dry THF at -23 °C. The mixture was stirred for 20 min and then the half of it was worked up by pouring into cold NaHCO₃ 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 50 mg (54%) of aldehyde 69 (Rf 0.40). No ketal 65 was obtained.

Aldehyde 69: 200 MHz ¹H NMR (CDCl₃) δ 10.36 (1 H, s), 7.35 (1 H, s), 7.05 (1 H, d, J = 8.0 Hz), 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 (s), 1590 (s), 1500 (s), 1475 (s), 1250 (s), 1100 (s), 1030 (s), 980 (m), 975 (w) cm⁻¹.

Attempts to isolate the mesylate or to prepare the chloride with lithium chloride or triphenylphosphine chloride gave varying amounts of aldehyde 69. The reaction with triphenylphosphine/carbon tetrachloride gave ketal 68. Attempts to react the unsaturated 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 0-methylated acetal in THF at 25 °C for a few minutes. The same acetal was prepared by the treatment of acetal 66 with potassium hydride in THF/DMP (1:1) followed by quenching with methyl iodide: 200 MHz ¹H NMR (CDCl₃) 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 (2H, s); IR (neat) 2900 (s), 1595 (s), 1480 (bs), 1250 (s), 1100 (bo), 1015 (m), 995 (m), 940 (w), 855 (w), 800 (w), 725 (w) cm⁻¹.

Methyl β-Oxobenzo-1,3-dioxole-5-propanoate, 71. When the procedure of Hajos was modified, a mixture of 51.9 g (1.55 mmol) of 60% sodium hydride in mineral oil and 71 mL (0.387 mmol) of 25% potassium hydroxide 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 50.5 mL of dry THF and 6.9 mL (0.140 mmol) of dimethyl carbonate (dried with CaC₂) was added and the mixture was heated at 65 °C. The mixture was stirred for 24 h at 65 °C and then cooled to room temperature. The mixture was poured into a solution of 60% sodium hydride in mineral oil. The mixture was stirred for 4 h at room temperature. The mixture was quenched with dilute hydrochloric acid 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 NaHCO₃ solution, dried with MgSO₄, 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 (CDCl₃) δ 7.08 (1 H, s), 7.05 (1 H, s), 7.00 (1 H, s), 6.83 (1 H, d, J = 2.0 Hz), 6.65 (1 H, d, J = 2.0 Hz), 6.50 (2 H, s), 3.93 (2 H, s), 3.73 (3 H, s); IR (neat) 1725 (m), 1602 (m), 1595 (s), 1470 (s), 1220 (s), 1105 (s), 1010 (s), 920 (m), 860 (m) cm⁻¹.

Attempted Preparation of Mesylate or Halides of Benzhydro-65: 5-Methoxy-7-(3,4,5-trimethoxyphenyl)-5,7-di-[hydrofuro[3,4-f]-benzo-1,3-dioxole-5-methanol, 66. To a solution of the acetal 65 (341 mg, 1.12 mmol) in 50 mL of dry THF at -78 °C under a nitrogen atmosphere was added dropwise tert-butyllithium (11.0 M solution and extracted three times with ether. The ether phase was washed three times with water and once with brine, dried over MgSO₄, and evaporated in vacuo to give 170.3 g (99%) of pure acetal 64 which solidified on cooling. An analytical sample was prepared by filtration and concentrating under reduced pressure, the crude product was recrystallized in ethanol from hexane to give 3.4 g (77%) of 66 as pale yellow crystals: mp 123-125 °C; 200 MHz ¹H NMR (CDCl₃) δ 10.36 (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 (s), 1590 (s), 1475 (s), 1250 (s), 1100 (s), 1030 (s), 980 (m), 975 (w) cm⁻¹.

Methyl β-Oxobenzo-1,3-dioxole-5-carboxaldehyde, 69. Via PBr₃. 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 PBr₃ (0.006 mL, 0.0693 mmol, distilled over CaH₂) and the solution was 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 NaHCO₃ solution and evaporated twice with methylene chloride. The ether phase was washed three times with water and once with brine, and evaporated to give 8.3 mg 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 (CDCl₃) 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), 3.55 (1 H, s), 3.87 (9 H, s), 3.85 (6 H, s), 3.45 (3 H, s); IR (neat) 3400 (bm), 2920 (s), 1580 (s), 1470 (s), 1220 (s), 1105 (s), 1010 (s), 920 (m), 860 (m) cm⁻¹.

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 130 mL of n-butyl lithium (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 CaH₂) 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 (289 mg, 3.09 mmol, oven dried) in 4 mL of dry THF at -23 °C. The mixture was stirred for 20 min. The mixture was poured into cold NaHCO₃ 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 50 mg (54%) of aldehyde 69 (Rf 0.40). No ketal 65 was obtained.
(6 H, s); IR (neat) 1720 (s), 1600 (cm$^{-1}$). Anal. Calcd for C$_{24}$H$_{22}$O$_5$: C, 65.08; H, 4.20. Found: C, 65.27; H, 4.01.

**Preparation of Silany 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 (35.0 mL, 350 mmol) at $-175$°C. 200 mL of dimethyl sulfoxide was added to the solution and then cooled to $-78$°C and the indanone (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 trifluoromethanesulfonate (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 evaporated in vacuo to give 12.2 g (100%) of the crude silyl enol ether as a yellow foam: 200 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.131 (1 H, d, $J$ = 1.1 Hz), 6.065 (1 H, d, $J$ = 6.4 Hz), 6.949 (1 H, d, $J$ = 6.4 Hz), 6.450 (1 H, d, $J$ = 6.4 Hz), 6.571 (1 H, s), 6.491 (2 H, s), 7.128 (1 H, s), 6.077 (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 (cm$^{-1}$). Anal. Calcd for C$_{24}$H$_{22}$O$_5$: C, 63.00; H, 5.00. Found: C, 63.07; H, 4.92.

**trans-5,7-Dihydroxy-(3,4,5-trimethoxyphenyl)-5H-indeno[5,6-d]-1,3-dioxole-7-one, 75.** Via Silyl Enol Ether. To a mechanically stirred solution of the above silyl enol ether (11.8 g, 28.4 nmol) 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 p-toluenesulfonyl chloride in dry benzene-acetic acid (7.5 g, 36.9% in 200 mL of methylene chloride) and then stirred 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$_2$CO$_3$ solution, 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 $^1$H NMR (CDCl$_3$) $\delta$ 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), 4.146 (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 (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-butylthiolium (9.55 mL of 1.62 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 nitrogen atmosphere was added MoOP$_3$ (8.7 g, 19.3 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$_2$O showed that the formation of the enolate would be over 97%. Excess MoOPH, inverse addition of D$_2$O and triethylamine could be reduced by using less triethylamine. Excess MoOPH, inverse addition, or lower temperature ($-44$°C) did not improve the yield. A model study with d-camphor gave 61% $^{1}$-hydroxylation.

**trans-6,7-Dihydro-6-[(methylsulfonyl)oxy]-7-(3,4,5-trimethoxyphenyl)-5H-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 nitrogen atmosphere was added directly methanesulfonyl chloride (8.049 mL, 8.388 mmol, distilled over CaH$_2$) in 100 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 $^1$H NMR (CDCl$_3$) $\delta$ 7.162 (1 H, s), 6.657 (1 H, s), 6.402 (2 H, s), 6.127 (1 H, d, $J$ = 1.0 Hz), 6.193 (1 H, s), 6.107 (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 (cm$^{-1}$); mass spectrum (70 eV), m/e 436 (M$^+$, 38), 342 (12), 341 (26), 340 (M$^+$ - CO$_2$, 100), 325 (11), 78 (4); high-resolution mass spectrum (70 eV), m/e 436.0834, calcd. for C$_{25}$H$_{23}$O$_7$S$_2$: 436.0829.

The sulfonate 77 (2.171 g, 4.54 mmol) in 20 mL of THF was cooled to $-78$°C, then 1.79 mL (12.9 mmol) of dry triethylamine was added slowly. After 0.5 h at $-78$°C, a solution of trimethylsilyl trifluoromethanesulfonate (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 evaporated in vacuo to give 12.2 g (100%) of the crude silany silyl enol ether as a yellow foam: 200 MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.634 (1 H, s), 6.683 (1 H, s), 6.380 (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), 3.809 (3 H, s), 3.790 (6 H, s), 0.334 (9 H, bs); IR (neat) 2920 (s), 1580 (s), 1430 (s), 1240 (s), 1105 (s), 1030 (s), 900 (m), 850 (s), 720 (m cm$^{-1}$).
Mesylate 78: 200 MHz 1H NMR (CDCl3) 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), 4.858 (1 H, d, J = 7.9 Hz), 4.461 (1 H, d, J = 10.8 Hz), 3.857 (3 H, s), 3.830 (6 H, s), 2.610 (6 H, s), 1.699 (3 H, s); IR (neat) 3400 cm⁻¹; mass spectrum (70 eV), m/e 435 (M⁺, 12), 434 (M⁺ - H₂O, 52), 356 (M⁺ - MeSO₂H, 38), 355 (M⁺ - MeSO₂H - H, 100), 354 (18), 338 (M⁺ - CO₂Me, 30), 267 (84), 313 (109), 312 (93). 278 (48), 265 (65), 264 (65), 157 (13), 135 (21), 115 (21), 105 (31). Anal. Calcd for Cl₈H₁₆N₂O₆: C, 57.95; H, 4.35; N, 15.46. Found: C, 57.97; H, 4.37; N, 15.43.

Dione 79: yellow solid; mp 224–226 °C dec; 200 MHz 1H NMR (CDCl3) δ 7.931 (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); 13C NMR (CDCl3) δ 128.25, 125.75, 124.75, 123.74, 122.54, 121.67, 120.34, 119.34, 118.44, 116.42, 115.43, 109.18, 103.41, 60.92, 56.37, 52.37; IR (neat) 1750 (cm⁻¹), 1700 (cm⁻¹); mass spectrum (70 eV), m/e 356 (M⁺, 41), 325 (M⁺ - CO₂, 47), 313 (30), 298 (21), 297 (20), 253 (16), 84 (17), 63 (17).

trans-6,7-Dihydro-6-[(p-toluenesulfonyl)oxy]-7-(3,4,3,5-trimethoxyphenyl)-5H-indeno[6,5-d]-1,3-dioxole-5-one and Dione 79. A solution of the alcohol 78 (85 mg, 0.237 mmol) in 8 mL of dry THF was cooled to –78 °C under a nitrogen atmosphere and added dropwise 136 mL (91.3 mmol) of bleach (37%). The mixture was then stirred for 2 h at –78 °C, and 10.8 mL of 1 N KOH and 1 L of H2O. The aqueous majority (70%) of the solvent was removed and water was added to give a yellow solid. The solution was then taken onto a preparative TLC (SiO₂, 3:2 hexane-ethyl acetate) to give the pure alcohol (50 mg, 100% yield).

When the procedure of Cava et al. was modified, a solution of the diazo ketone 83 was obtained, which decomposed completely after 3 h in refluxing benzene. When the procedure of Cava et al. was modified, a solution of the diazo ketone 83 was obtained, which decomposed completely after 3 h in refluxing benzene.

5-Methyl-7-(3,4,5-trimethoxyphenyl)-5H-indeno[6,5-d-]1,3-dioxole-5-one. A solution of 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 (0.261 mmol) in 370 mL (296 mmol) of 1 N KOH. The mixture was heated 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 84 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 1H NMR (CDCl3) δ 7.211 (1 H, s), 6.641 (1 H, d, J = 10.8 Hz), 6.500 (1 H, d, J = 10.8 Hz), 6.050 (1 H, d, J = 10.8 Hz), 5.948 (1 H, d, J = 1.1 Hz), 3.822 (3 H, s); IR (neat) 2075 (s), 1680 (cm⁻¹). UV (MeOH) λmax 344 (18,000), 314 (8800), 270 (9200), 231 (24000 nm); λ 360 (4800), 405 (552) nm; UV (dioxane) λmax 372 (10000), 340 (17,000), 314 (9900), 274 (12000), 232 (35000) nm; mass spectrum (70 eV), m/e 368 (M⁺, 25), 342 (34), 341 (31), 240 (M⁺ - CO₂, 90%), 229 (35), 228 (23), 227 (25), 211 (32); high-resolution mass spectrum (70 eV), m/e 368.1002, calcd for C₂₈H₂₈N₂O₈ 368.1008.

Then, 0.5 mL of 3% n-butyllithium (172 mL of 1.52 M solution, 0.261 mmol) in hexane was added to a solution of potassium tert-butoxide (24 mg, 0.214 mmol) in 100 mL of ethanol. Isoamyl nitrite (8.80 mL, 65.8 mmol) was added as a cold solution of the y-keto ester formed by insertion of the a-keto carbene from the y-keto ester. The y-keto ester was then treated with 2 equiv of NaHCO₃, 0.8% of the acid corresponding to the y-keto ester was collected, and the remaining alcohol was washed with water, dried over MgSO₄, and evaporated in vacuo to give 15.5 g (95%) of oxime in 100 mL of ethanol. The reaction was then treated with 2 equiv of n-butyllithium (172 mL of 1.52 M solution, 0.261 mmol) in hexane and 2 equiv of n-butyllithium (172 mL of 1.52 M solution, 0.261 mmol) in hexane. The reaction was then treated with 2 equiv of n-butyllithium (172 mL of 1.52 M solution, 0.261 mmol) in hexane. The reaction was then treated with 2 equiv of n-butyllithium (172 mL of 1.52 M solution, 0.261 mmol) in hexane. The reaction was then treated with 2 equiv of n-butyllithium (172 mL of 1.52 M solution, 0.261 mmol) in hexane.
(B) Temperature. Lowering the temperature to -28 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 (cut off at 345 nm) was used, a lower yield of 84 was obtained. (2) When 4,4′-biphenylamine (dimethylamino)benzophenone (16 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 (cut off at 406 nm) was used and the photolysis carried out for 3 h at 0 °C, 60% of the diazirene 86 was isolated: mp 147-150 °C dec; 200 MHz 1H NMR (CDCl3) δ 7.225 (1 H, s), 6.740 (1 H, s), 6.245 (2 H, s), 6.116 (2 H, 0.414 (1 H, s), 3.830 (3 H), 3.803 (6 H); IR (neat) 3200 (cm-1); mass spectrum (70 eV), m/e 345 (M+1, 100), 327 (70), 288 (17), 284 (3), 210 (70), 181 (20), 155 (9), 95 (27), 53 (18), 31 (16), 19 (5). Anal. Calcd for C61H64CdO2: C, 81.67; H, 5.65. Found: C, 81.50; H, 5.46.

4-Carboximethoxy-3-(3,4,5-trimethoxyphenyl)-3a,6a,8b,10b-tetrahydrofuraz[3,4,5-b]naptho[2,3-d][1,3]-dioxol-2(3H)-one, 2a and 2b. The diethylamine solution of the crude reaction product was neutralized to pH 1 with 10% aq. HCl. The resulting suspension was extracted with 10% aq. NaOH and the organic phase was evaporated to dryness.

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Registry No. 5, 29576-13-4; 15, 15930-53-7; 16, 7748-58-5; 17, 56251-58-2; 18, 94670-72-1; 19a, 94670-74-3; 19b, 94670-76-7; 20a, 94670-77-6; 20b, 94706-16-8; (±)-21, 94670-78-7; (±)-22, 94670-79-8; (±)-26, 94670-80-1; 27, 27452-05-5; (±)-28, 89203-87-6; (±)-29, 94670-81-2; (±)-30, 94670-92-3; 31, 94670-83-4; 32, 26757-78-8, 34, 91-10-1; (±)-35, 94670-84-5; (±)-36a, 94670-85-6; (±)-36b, 94670-86-7; 37, 7115-91-5; 41, 1449-46-4; 42E, 94670-88-9; 42Z, 94670-87-8; (±)-43, 94706-16-8; (±)-44, 94670-89-0; 45, 40084-81-7; (±)-46, 94670-90-3; 47, 452806-34-5; 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; (±)-58, 94670-98-1; (±)-59, 94670-99-2; 61, 94671-00-8; 62a, 94671-01-9; 63, 94671-02-0, 64, 74979-22-4; 66, 58-61-7; 67, 75101-84-7; 68 (mesylate), 94671-03-1; 68 (methyl ether), 94671-04-2; 69, 94671-05-3; 69, 94671-06-4; 70, 3162-29-6; 71, 50413-35-7, 72, 94671-07-5; 73, 94671-08-6; (±)-74, 94671-09-7; (±)-74 (trimethylsilyl enol ether), 94671-10-0; (±)-75, 94671-11-1; (±)-75 (tosylate), 94671-12-2; (±)-76, 94671-18-0; (±)-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, 94671-19-1; (±)-84 (cy clohexylamide), 94671-19-9; 85, 94671-20-2; (±)-86, 46671-21-3; (±)-87, 94671-22-4; (±)-90, 94671-23-5; (±)-92, 94671-24-6; (±)-93, 94703-94-6; CH₃CHO, 108-05-4; NCCO₂H₂, 372-09-8; furan, 110-00-9; cyclopentadiene, 542-92-7; 6-amino-benzono-1,3-dioxol-5-carboxylic acid, 20332-15-6; 3-(3-bromobenzoyl-1,3-dioxol-5-y1)-2-cyanopropionic acid pyridine salt, 94671-26-8; 4-bromo-2,6-dimethylphosphonate, 70654-71-6.