Heteroatom Directed Photoarylation. Synthetic Potential of the Heteroatom Oxygen

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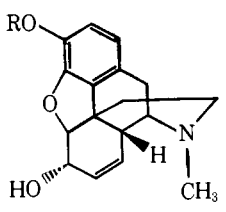
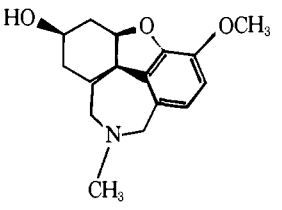
Abstract: A series of 2-aryloxyenones **5a–u** is prepared by reaction of the appropriate phenol with isophorone epoxide and base in refluxing tetrahydrofuran–hexamethylphosphoramide solution. Photocyclization–rearrangement of **5** gives dihydrofurans **17** in high yield. The effect of substituents on the aromatic ring on photocyclization is noted. As with aryl vinyl sulfides, fused ring aryloxyenones derived from octalone epoxides give photoproducts with only a *cis*-decalone ring fusion. An annelation reagent **12** is prepared from aryloxyacetic acid salts and vinyl Grignard reagents; annelation of ethyl 2-cyclohexanonecarboxylate with **12a** gives aryloxyenone **10b**, and annelation of **13** gives the potential morphine intermediate **15**. Stereochemistry of heteroatom directed photoarylation is demonstrated in irradiation studies with **15**; in benzene, **15** gives only **24** with a *trans*-dihydrofuran ring fusion, while irradiation in benzene–methanol solution gives both **24** and *cis*-dihydrofuran **25a**. Thus, intermediate carbonyl ylide **23** undergoes suprafacial 1,4-hydrogen migration in aprotic (benzene) solution, but in protic (methanol) solution, competitive protonation of the ylide with solvent (methanol) leads to the more stable **25a** as well. Reductive cleavage of **17a** gives the hemiketal **30** and that from **24** or **25** gives lactone **29**. On the other hand, Baeyer–Villiger oxidation of **17a** gives only lactone **32**. Lactone **32** undergoes titanium tetrachloride induced rearrangement to benzofurancarboxylic acid **33** (98%) at −78 °C in methylene chloride; at reflux temperature, tricyclic ketone **34** is the reaction product (94%). Similarly, photoproduct **21** is converted to lactone **37** and thence to tetracyclic ketone **40**. The methyl substituted furan carbon–carbon double bond in **34** represents a latent ketone carbonyl group from which diketone **41** is liberated by ozonolysis. Simple reactions coupled to the oxidative cleavage allow for completely regioselective preparation of monoketones **42** and **43** as well. Treatment of lactone **30** with sodium methoxide in methanol gives methyl ester hemiacetal **36b**, which is converted to methyl ester thioacetal **44**. Desulfurization with formation of a methyl group gives the δ-aryl substituted alkanoic ester **45**.

In the preceding paper[3] we present a detailed study of the synthetic potential of heteroatom directed photoarylation with aryl vinyl sulfides. The method provides an efficient and experimentally simple route to aryl annelated dihydrothiophenes. Extension of the method to include the heteroatom oxygen is especially attractive, because of the potential for synthesis of a variety of medicinally important natural products. Indeed, we feel that heteroatom directed photoarylation with aryl vinyl ethers offers a conceptually unique route to the morphine alkaloids **1**, the galanthamine-type alkaloids found in plants of the *Amaryllidaceae* such as lycoramine (**2**), and perhaps even the hasubanan alkaloids, e.g., cepharamine (**3**).



1a, R = H (morphine)
b, R = CH_3 (codeine)



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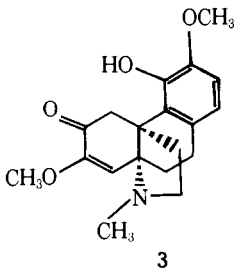

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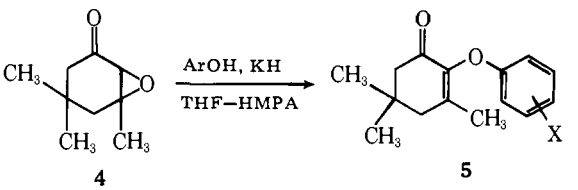
A complete review of aryl ether photochemistry will not be attempted here;[4] we will note, however, that at the outset of this work, reported photoreactions of aryl ethers consisted of cleavage of the ether bond(s) followed by hydrogen abstraction from solvent to give phenols and photorearrangement to give ortho- and para-substituted hydroxybiphenyls.[5] Photocyclization–elimination of ortho-substituted diaryl ethers had been accomplished in low to moderate yield;[6] more recently, the oxidative photocyclization of diphenyl ether to dibenzofuran has been reported.[7]

Careful considerations of reported aryl ether photochemistry and the efficiency of dihydrothiophene formation from 2-thioaryloxyenones[3] suggested that our studies should begin with the photochemistry of 2-aryloxyenones.

Results and Discussion

Thioaryloxyenones may be prepared in nearly quantitative yield by base-catalyzed reaction of an aryl mercaptan with 1 equiv of an epoxy ketone in protic solvents at or below room temperature. Because of decreased nucleophilicity of phenoxide relative to thiophenoxide, more vigorous conditions were required to effect epoxide opening with phenols. Potassium hydride (0.1 equiv) assisted reaction of epoxide **4** with 1.1 equiv of phenol in refluxing tetrahydrofuran (THF) solution containing 0.75 equiv of hexamethylphosphoramide (HMPA) gave analytically pure aryloxyenone **5** in 92% isolated yield. This procedure was found to be generally useful and a variety of 2-aryloxyenones could be prepared in excellent yield (Table I).

We note that a wide range of functionality in the phenol is compatible with the conversion **4** → **5**. Phenols with bulky



4 **5**

substituents at an ortho position, such as 2-*tert*-butyl-5-methylphenol, may be utilized. Furthermore, phenols with an electron-withdrawing substituent, which might be expected to reduce phenoxide nucleophilicity, are sufficiently reactive to give aryloxyenones in high yield; the single exception is 2-

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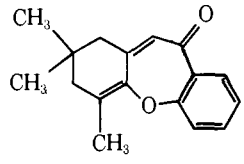
carbomethoxyphenol, which failed to react with epoxide **4** under a variety of reaction conditions.

Reaction of 2-hydroxyacetophenone with **4** gives 2,2,4-trimethyl-2,3-dihydrodibenz[*b,f*]oxepin-10(1*H*)-one (**6**), pre-



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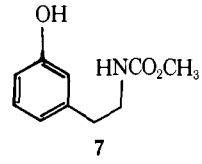

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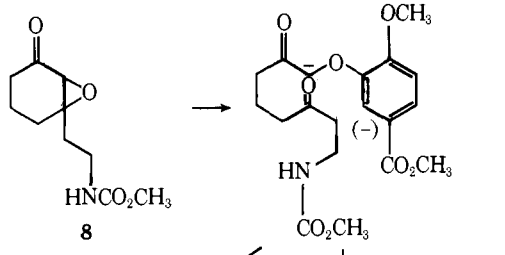
sumably via cyclization–dehydration of intermediate aryloxyenone **5m.**

Monocyclic aryloxyenones are prepared in excellent yield when the substituent at C(3) in the epoxy ketone is either hydrogen or methyl. With a larger alkyl group at C(3), competing reactions may become important. In our total synthesis of lycoramine **2**,[8] epoxy ketone **8** underwent reaction with the po-



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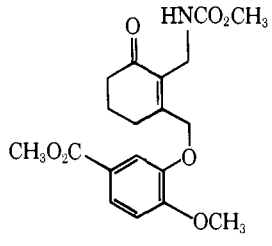
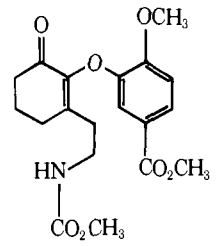


9b

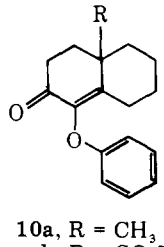


9a

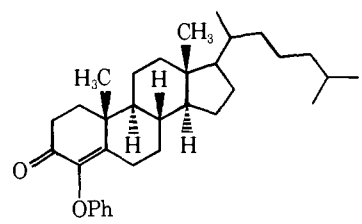
tassium salt of 5-carbomethoxy-2-methoxyphenol to give a mixture of the desired aryloxyenone **9a** (~50%) and the isomeric **9b** (15%). The formation of both **9a** and **9b** is explained by consideration of an intermediate diketone enolate, from which cyclization–dehydration may occur to give either **9a** or **9b** as shown.[9]

Aryloxyenones derived from 2-cyclohexen-1-ones, which do not have a geminally substituted ring carbon atom, are somewhat unstable to the strongly basic reaction conditions required for their preparation. For example, elimination of 5-carbomethoxy-2-methoxyphenol from **9a** to give phenol **7** occurs to the extent of ~5% during preparation of **9a.**

Multicyclic aryloxyenones also are available by utilization of the epoxy ketone method. In this way, aryloxyenones **10a**



10a, R = CH_3
b, R = CO_2Et



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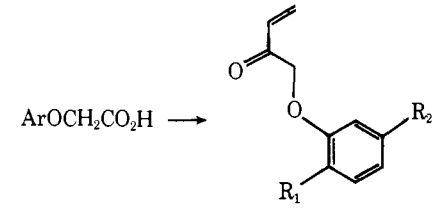
and **11** were prepared in excellent yield. With fused ring aryloxyenones, competing reactions to give isomeric by-products do not occur, presumably because of ring strain associated with products analogous to **9b** in reactions leading to **10a** and **11.**

Octalones of the type used in construction of **10a** are generally prepared by annelation of the appropriate cycloalkanone with methyl vinyl ketone. A potentially more efficient method for preparation of fused ring aryloxyenones would incorporate the aryloxy functionality in the ring annelation reagent.[10] Aryloxymethyl vinyl ketones **12a** and **12b** were prepared by

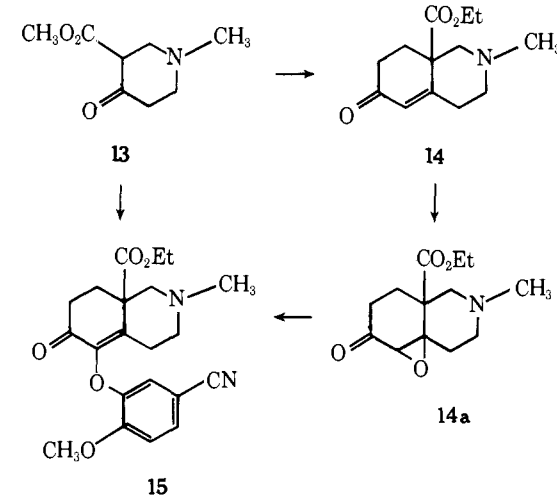


12a, $R_1 = R_2 = H$
b, $R_1 = OCH_3$; $R_2 = CN$

reaction of the carboxylate salt of the appropriate aryloxyacetic acid with vinylmagnesium bromide. Annelation of ethyl 2-cyclohexanonecarboxylate with 1-phenoxy-3-buten-2-one **12a** gave **10b** in good overall yield (see Experimental Section).

A comparison between the direct annelation and the epoxy ketone route to fused ring aryloxyenones was made in our approach toward the total synthesis of morphine (Scheme I).[11]

Scheme I



13

14

14a

15

Annelation of piperidone **13**[12] with methyl vinyl ketone gave enone **14,** which was epoxidized with basic hydrogen peroxide. Reaction of the resulting epoxy ketone **14a** with 3-hydroxy-4-methoxybenzonitrile gave aryloxyenone **15** in 31% overall yield from **13.** On the other hand, piperidone **13** was converted to **15** by annelation with aryloxymethyl vinyl ketone **12b** in 43% isolated yield.

Pyrex-filtered irradiation of **5a** has been performed on a 20-g scale in degassed benzene–methanol–acetic acid solution (1:1:1) and *cis*-dihydrofuran **17a** was formed in 95% yield. Partition of the photoreaction between ether and 1 N sodium hydroxide and acidification of the sodium hydroxide layer gave phenol **19** in 2% isolated yield.

The photoreaction of **5a** is analogous to that of the sulfur analogue previously described,[3] in that irradiation of **5a** in pure benzene solution leads to a more complicated product distribution. The major reaction product, however, is *trans*-dihydrofuran **18.** Treatment of the photoreaction mixture with sodium carbonate in benzene–methanol solution results in epimerization of **18** to the *cis*-dihydrofuran **17a.**

Table I. Preparation and Irradiation of 2-Aryloxyenones

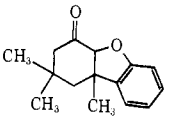
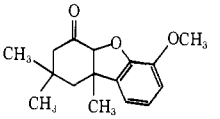
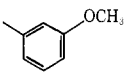
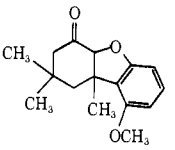
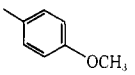
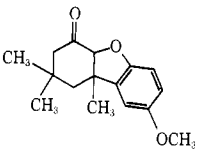
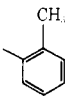
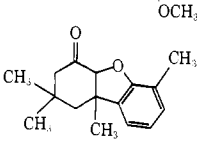
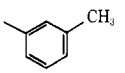
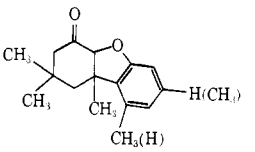
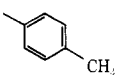
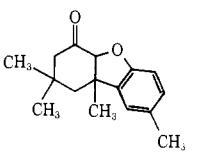
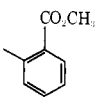
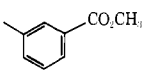
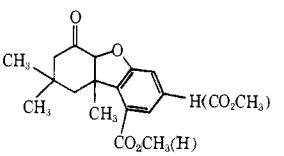
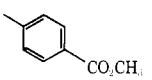
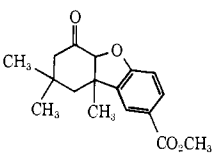
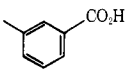
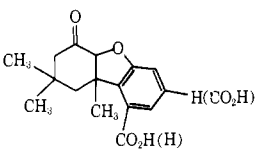
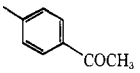
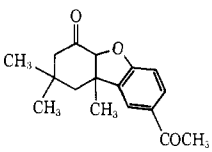
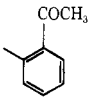
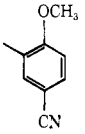
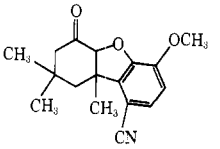
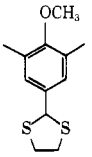
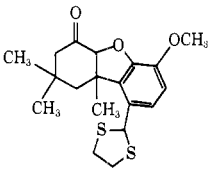
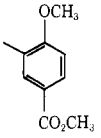
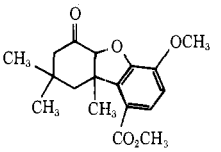
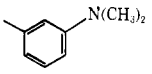
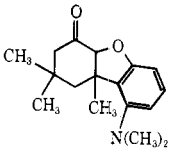
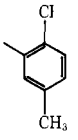
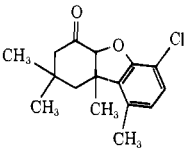
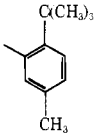
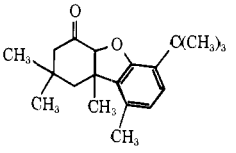
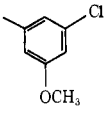
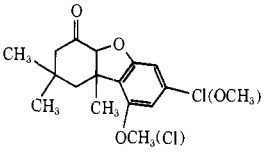
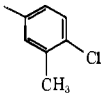
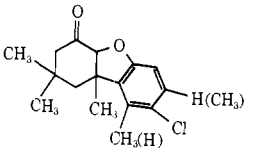
2-Aryloxyenone	Ar	% yield[a] of **5**	Dihydrofuran **17** formed	% yield[b] of **17**
5a		92		95[c] (88)
b		87		30[d]
c		90		92[c] (90)
d		89		32[c]
e		91		91[c] (80)
f		86		100[d]
g		82		91[c] (80)
h		0		
i		90		100[d]
j		87		100[d] (100)
k		95[e]		100[d]
l		88		(94)

Table I (*Continued*)

2-Aryloxyenone	Ar	% yield[a] of **5**	Dihydrofuran **17** formed	% yield[b] of **17**
m		78[f]		
n		74		100[c] (87)
o		62		58[c] (40)
p		90		100[c] (95)
q		50		
r		85		(83)
s		72		(85)
t		97		100[d]
u		90		100[d]

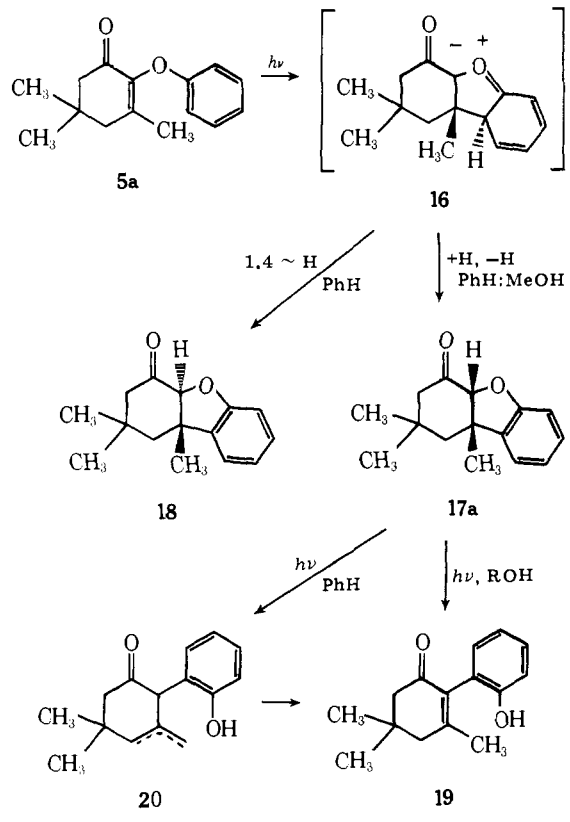
[a] Isolated yields. [b] Analysis by ^{1}H NMR or VPC as indicated. Yields in parentheses refer to isolated yields. [c] Analysis by VPC. [d] Analysis by ^{1}H NMR. [e] Prepared by saponification of **5i**. [f] Isolated product was 2,2,4-trimethyl-2,3-dihydrodibenz[*b,f*]oxepin-10(1*H*)-one (**6**).

A probable mechanism for photocyclization of **5a** in benzene solution involves conversion of **5a** to carbonyl ylide **16**, from which suprafacial 1,4-hydrogen migration gives the trans-fused dihydrofuran **18**. We presume that in protic solvents, *cis*-dihydrofuran **17a** is formed by protonation of the carbonyl ylide followed by rearomatization via deprotonation. Alternatively, **16** may rearrange to **18** and **18** may epimerize to the more stable **17a**.[3]

Control experiments indicate that phenol **19** is not produced directly from **5a**, but rather arises from a secondary photoreaction of **17a**. Irradiation of **17a** in aprotic solvents (e.g., benzene) leads to a mixture of β,γ-unsaturated ketones **20**, which are isomeric with **19**. Subjecting the mixture **20** to reaction conditions used in formation of **19** from **17a** results in rearrangement to **19**. Thus, **20** apparently is an intermediate in the photoconversion **17a** → **19**. A discussion of the scope and mechanism of benzodihydrofuran photorearrangements will be presented elsewhere.

Pyrex-filtered irradiation of the series of aryloxyenones **5a–u** in degassed benzene–methanol–acetic acid solution generally gave *cis*-dihydrofurans in excellent yield (Table I). Both electron-withdrawing and weakly electron-releasing substituents on the aromatic ring are compatible with efficient photocyclization. However, strongly electron-releasing substituents present some problems. With **5q**, in which there is a *m*-dimethylamino group, cyclization does not occur, but rather **5q**

Scheme II

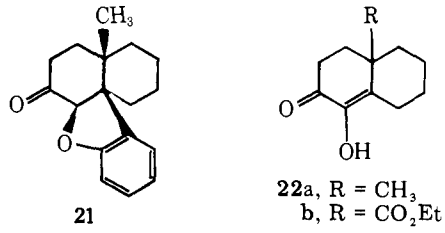


undergoes slow photopolymerization. The *o*-methoxy and *p*-methoxy analogues **5b** and **5d** give dihydrofurans in low yield; however, *m*-methoxy substituted **5c** gives **17c** in 92% yield. The conversion **5c** → **17c** is extremely interesting because of the possibility of production of two regioisomers. Only the dihydrofuran resulting from cyclization ortho to the methoxy substituent was detected; however, with a *m*-methyl (**5f** and **5u**), *m*-carbomethoxy (**5i**), or *m*-carboxylic acid function (**5k**), photocyclization leads to ~2:1 mixture of regioisomers, with the 1,2,3 substitution predominating. Remarkably, the powerful directing effect of the *m*-methoxy group is completely offset by a chloro substituent at the other meta position (e.g., **5t**). On the other hand, changes in solvent composition have no effect on regioisomer distribution (see Experimental Section). Observations such as these should provide insight into the electronic distribution in the excited state of **5** and further work in this area is in progress.

Fortunately, the adverse effects of strongly electron-releasing substituents may be overcome by positioning electron-withdrawing groups meta to the phenolic ether function. Thus, the 2-methoxy-5-cyano and 2-methoxy-5-carbomethoxy analogues **5n** and **5p** give dihydrofurans **17n** and **17p**, respectively, in essentially quantitative yield. This discovery has been extremely important in total synthetic plans for lycoramine **2** and the morphine alkaloids.

Aryloxyenone **5r** is interesting because photocyclization occurs to give only **17r**, with no evidence for cleavage of an aryl-halogen bond. This result, coupled with the fact that halogen may be efficiently removed from aromatic rings by hydrogenolysis or lithium aluminum hydride reduction, illustrates the useful concept of halogen serving as a blocking group to control regioselectivity of photocyclization of meta-substituted aryloxyenones.

Pyrex-filtered irradiation of **10a** in degassed benzene solution saturated with *p*-toluenesulfonic acid gave dihydrofuran **21** in 90% isolated yield and diketone **22a** (4–5%). Significantly, only dihydrofuran **21** with a *cis*-decalone ring system



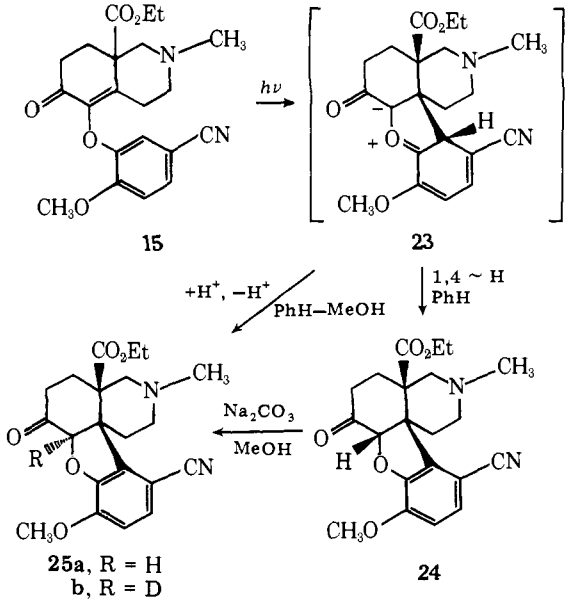
was isolated and none of the isomeric dihydrofuran with a *trans*-decalone ring junction could be detected. From combined VPC and ^{1}H NMR spectral limitations, the stereoselectivity of photocyclization of **10a** was estimated to be at least 90:1. The origin of the remarkable stereoselectivity encountered with heteroatom directed photoarylation has been presented[3,13] and will not be discussed here.

Photocyclization of certain fused-ring aryloxyenones in aprotic solvents leads to exclusive formation of *trans*-dihydrofurans. For example, irradiation of **15** in benzene solution gave the tetracyclic morphine structural analogue **24** in >90% yield (Scheme III). On the other hand, irradiation of **15** in benzene–methanol solution (1:1) gave **24** and cis-fused dihydrofuran **25a** (1.3:1, respectively. That these two photoproducts are epimers was established by quantitative conversion of **24** into **25a** in methanolic solution saturated with sodium carbonate. Furthermore, irradiation of **15** in benzene–methanol saturated with sodium carbonate gave only **25a** in 88% isolated yield.

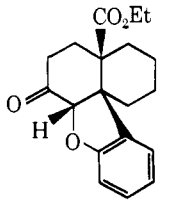
Irradiation of **15** in methanol-d_1 gave **24** with no incorporation of deuterium and **25** with complete deuteration at C(1). Control experiments revealed that while **24** was completely stable to the photolysis conditions, **25a** underwent proton exchange with methanol-d_1 to give **25b**.

These experiments allow us to present a mechanism for photocyclization of fused-ring aryloxyenones (Scheme III). That is, **24** and **25a** are formed by unique conrotatory photocyclization of **15** to carbonyl ylide **23**; the other possible conrotatory mode leading to a *trans*-azadecalone ring fusion does not operate.[3] With the assumption that cyclization of **15** to give only **23** occurs in both protic and aprotic solvents, then suprafacial 1,4-hydrogen migration in **23** gives the strained trans-fused dihydrofuran **24**, while competitive protonation–deprotonation of the ylide in protic solvents gives the more stable epimer **25a**.

Scheme III



Additional studies with **10b** and **11** reflect the generality of exclusive *cis*-decalone formation in photocyclization of these fused-ring aryloxyenones. Both **26** and **27** were formed on irradiation of **10b** in benzene–methanol–acetic acid solution; similarly, steroid derivative **11** gave a photoproduct analogous to **27**. Treatment of **26** and **27** with 1 N potassium hydroxide in methanol followed by acidification gave a single lactol **28**.



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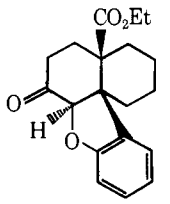

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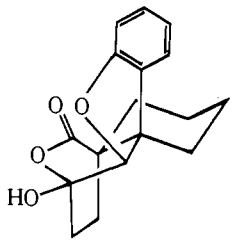

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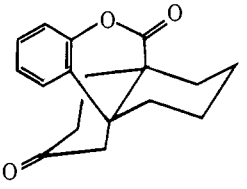


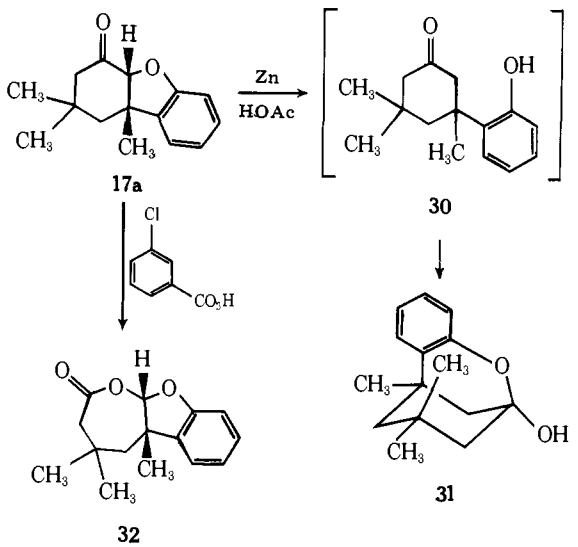
29

In contrast to **10a, 11,** and **15,** extensive ether cleavage to give **22b** (35%) occurred on photolysis of **10b.** Formation of **22b** does not occur from the triplet state of **10b,** because irradiation in the presence of the triplet sensitizer benzophenone in benzene solution gave only *trans*-dihydrofuran **27** (67% isolated yield) and no α-diketone **22b.**

The general synthetic utility of heteroatom directed photoarylation in preparation of aryl annelated dihydrofurans had been established. An outstanding feature of the synthesis is the ability to form a carbon–carbon bond from an aromatic ring to an angular carbon atom that may be located at a ring junction. We next turned our attention to development of methodology which was to exploit this important synthetic tactic.

Keto dihydrofuran **17a** undergoes quantitative reductive cleavage of the C(2)–oxygen bond with zinc dust in refluxing acetic acid solution to give the ortho-substitutued phenol **30,** isolated as hemiketal **31** (Scheme IV). This experiment suggests that the hasubanan alkaloids (e.g., cepharamine **3**) may be accessible by heteroatom directed photoarylation of an appropriate aryloxyenone, followed by reductive cleavage to give the required phenolic ketone functionality. In this regard, treatment of the structurally more complicated **26** or **27** with zinc dust in refluxing propionic acid solution gave a single keto lactone **29** in high yield. With this experiment, the stereochemistry of the decalone ring fusion in **26** and **27** becomes apparent; only a photoproduct with a *cis*-decalone ring fusion is capable of generating a lactone on reductive cleavage of the C(2)–ether oxygen bond. The structure of other photoproducts derived from fused-ring aryloxyenones rests principally on similar chemical reactivity and ^{1}H NMR spectral data for the C(2) hydrogen, for which resonance generally occurs at δ 4.4–4.5.

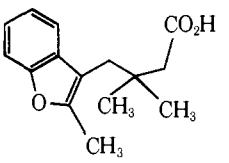
Scheme IV



17a **30** **31** **32**

Baeyer–Villiger oxidation of **17a** was accomplished with *m*-chloroperbenzoic acid and, as expected,[14] only lactone **32** was formed in essentially quantitative yield. With this oxidative cleavage of the C(1)–C(2) bond in **17a,** we were able to explore the possibility of annelating the aromatic ring in **32** via the newly formed lactone acyl group.

The acylation, accompanied by rearrangement to a benzofuran, is accomplished by refluxing a methylene chloride solution of lactone **32** with excess titanium tetrachloride to give tricyclic ketone **34** in 94% isolated yield and carboxylic acid



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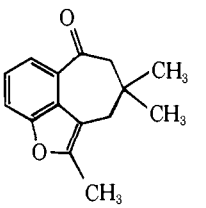

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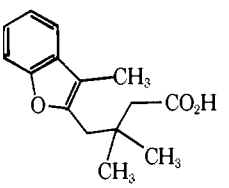

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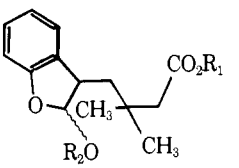
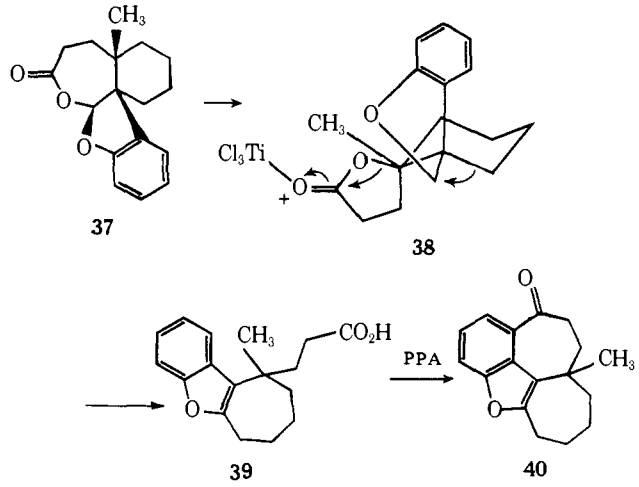


36a, $R_1 = CH(CH_3)_2$; $R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = R_2 = CH_3$

35 (1.4%). When the $TiCl_4$ reaction was performed at −78 °C, furancarboxylic acid **33** was the major reaction product (98%). Other Lewis acids such as stannic chloride induce rearrangement of **32** to **33;** however, substitution of titanium tetraisopropoxide results in lactone ring opening to give the isopropyl ester **36a.** Similarly, sodium methoxide in methanol gives the methyl ester **36b.** The rearrangement is not promoted by mineral acids, in that methanolic hydrogen chloride gives the methyl ester acetal **36c** and lactone **32** is recovered unchanged from its solution in refluxing methylene chloride saturated with hydrogen chloride.

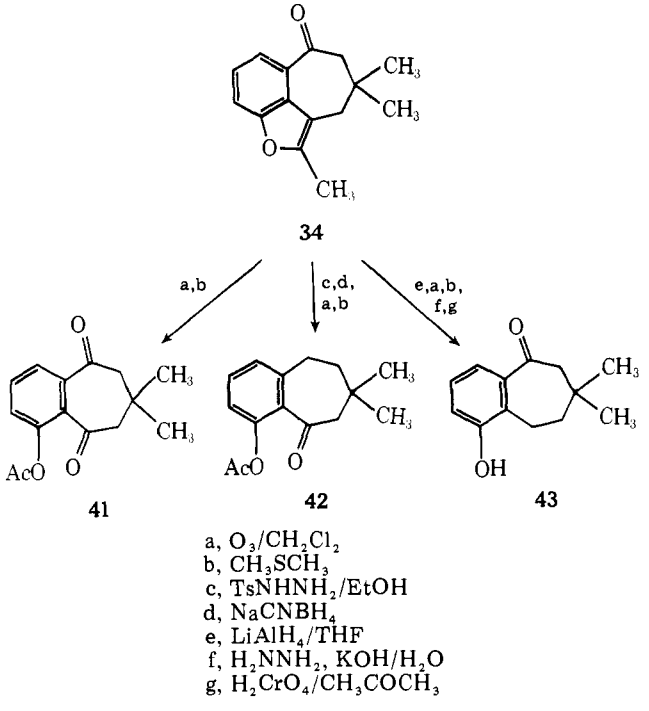
It is noteworthy that the $TiCl_4$-induced rearrangement **32** → **33** is highly stereoselective; the carbon chain (here, the C(3) methyl group) in an anti orientation to the leaving carboxylate function undergoes preferential migration to C(2). In order to examine the generality of this rearrangement, lactone **37** was prepared from tetracyclic dihydrofuran **21.** Treatment of **37** with 1.5 equiv of $TiCl_4$ in methylene chloride for 30 min gave tricyclic acid **39,** the product of bond migration anti to the departing carboxylate function as shown in presumed intermediate **38.** Polyphosphoric acid cyclodehydration of **39** gave the tetracyclic ketone **40.**

The methyl substituted furan carbon–carbon double bond in **34** represents a latent ketone carbonyl group, from which diketone **41** is liberated by ozonolysis. Furthermore, as shown



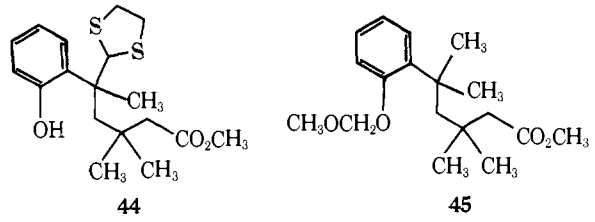
in Scheme V, simple reactions coupled to the oxidative cleavage sequence allow for completely regioselective preparation of monoketones **42** and **43** as well.

Scheme V



Thus, we have shown that phenols may be annelated with epoxides derived from 2-cycloalken-1-ones. The process is characterized by high regiochemical control, and we note that from an epoxide annelating reagent containing n ring atoms, $n-1$ atoms are incorporated into the new ring; only C(2) is excluded. The simplicity of experimental operations and high overall yields (~70% for the conversion of phenol to bicycle **41**) suggest that the method should be useful for annelation of complex carbocyclic ring systems to aromatic rings.[15]

We also have examined the possibility of converting the acetal carbon atom in **36b** into a methyl group. In this way, heteroatom directed photoarylation would be extended to include the potential for synthesis of δ-aryl alkanoic esters with the aromatic ring attached to an angular hydrocarbon center (e.g., **45**). To this end, **36b** was converted to cyclic thioacetal **44** in 91% yield with ethanedithiol and boron trifluoride etherate. Protection of the phenolic hydroxyl group in **44** with chloromethyl methyl ether followed by desulfurization with



Raney nickel in refluxing ethanol gave the desired methyl ester **45** in 75% yield.

Conclusion

Heteroatom directed photoarylation is a useful method for construction of a variety of aryl annelated dihydrofurans. The method has been used in total synthesis of the *Amaryllidaceae* alkaloid lycoramine (**2**),[8] and a tetracyclic morphine (**1a**) structural analogue.[11] Furthermore, methods have been presented for annelation of arcmatic rings (e.g., phenol → **41**) and synthesis of δ-aryl alkanoic esters (e.g., phenol → **45**), which feature heteroatom directed photoarylation as the key step in carbon–carbon bond formation. Once again, we must emphasize that with both sulfur and oxygen, the photoreaction generally proceeds with high chemical and photochemical efficiency, is compatible with a wide variety of functional groups within the molecular system, and may be effectively performed at high concentrations (~0.1 M). Similar methodology for the heteroatom nitrogen[16] has been developed and detailed results of this study will be presented in due course.

Experimental Section

2-Phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one (5a). General Procedure for Preparation of 2-Aryloxyenones from Epoxy Ketones. A solution of phenol (20 g, 0.21 mol) in freshly distilled THF was added to a stirred suspension of potassium hydride (3.50 g, 20 mmol, 22.5% KH in oil) in THF (10 mL) in a nitrogen atmosphere. After consumption of the KH, hexamethylphosphoramide (HMPA, 35 mL, 0.20 mol) and isophorone epoxide (**4**, 36 g, 0.23 mol) were added. The resulting solution was heated to reflux for 20 h, after which time analysis was performed on a 6 ft × ⅛ in. glass column filled with 5% SE-30 on Chromosorb W, 80–100 mesh size; temperature programmed 80 °C (2 min) to 160 °C (8 °C/min); retention time phenol, 3.6 min; **4**, 6 min; **5a**, 24 min. Water (50 mL) was added and the resulting mixture was washed with benzene–ether (1:1, 1 × 200 mL, 2 × 50 mL). The organic extract was washed with water (3 × 50 mL), dried over anhydrous magnesium sulfate, evaporated, and crystallized from ether–petroleum ether to give **5a** (47 g, 96%). Recrystallization gave analytically pure **5a** (45 g, 92%, mp 104–105 °C); ^{1}H NMR gave singlets at δ 1.13 (6 H), 1.87 (3 H), 2.40 (4 H), and a multiplet at 6.7–7.4 (5 H); IR (Nujol) 5.95, 6.08, 6.25, 6.32, and 8.18 μ; UV (methanol 218 nm (ε 16 400), 244 (15 900), 313 (510), and 366 (14); electron impact mass spectrum *m/e* 230.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88; O, 13.89. Found: C, 78.20; H, 7.89.

2-(*o*-Methoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5b) was prepared from *o*-methoxyphenol and epoxide **4** and crystallized from ether–petroleum ether (87%, mp 88.0–88.5 °C); ^{1}H NMR gave singlets at δ 1.13 (6 H), 1.91 (3 H), 2.39 (4 H), 3.92 (3 H), and a multiplet at 6.5–7.0 (4 H); IR (chloroform) 5.95, 6.08, 6.29, 8.03, 8.52, 8.95, and 9.75 μ; electron impact mass spectrum *m/e* 260.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; O, 18.44. Found: C, 73.85; H, 7.72.

2-(*m*-Methoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5c) was prepared from *m*-methoxyphenol and epoxide **4** (90%, bp 136–137 °C at 0.20 mm); ^{1}H NMR gave singlets at δ 1.13 (6 H), 1.87 (3 H), 2.40 (4 H), 3.76 (3 H), and multiplets at 6.29–6.67 (3 H) and 6.95–7.33 (1 H); IR (neat) 5.95, 6.08, and 6.22 μ.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; O, 18.44. Found: C, 73.74; H, 7.76.

2-(*p*-Methoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5d) was prepared from *p*-methoxyphenol and epoxide **4** (89%, bp 126–129 °C at 0.15 mm; crystallized on standing, mp 44–45 °C); ^{1}H NMR gave singlets at δ 1.12 (6 H) and 6.80 (4 H); IR (chloroform) 5.95, 6.08, 6.20, and 6.28 μ.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; O, 18.44. Found: C, 73.83; H, 7.75.

2-(*o*-Methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5e) was prepared from *o*-cresol and epoxide **4** (91%, bp 109–112 °C at 0.10 mm); ^{1}H NMR gave singlets at δ 1.13 (6 H), 1.88 (3 H), 2.39 (7 H, broad), and a multiplet at 6.35–7.30 (4 H); IR (neat) 5.95, 6.08, 6.22, and 6.30 μ.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.66; H, 8.25; O, 13.09. Found: C, 78.61; H, 8.16.

2-(*m*-Methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5f) was prepared from *m*-cresol and epoxide **4** and crystallized from ether–petroleum ether (86%, mp 57–58 °C); ^{1}H NMR gave singlets at δ 1.12 (6 H), 1.85 (3 H), 2.28 (3 H), 2.40 (4 H), and a multiplet at 6.44–7.30; IR (chloroform) 5.95, 6.08, 6.22, 6.30, and 8.00 μ.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.66; H, 8.25; O, 13.09. Found: C, 78.75; H, 8.33.

2-(*p*-Methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5 g) was prepared from *p*-cresol and epoxide **4** and crystallized from ether–petroleum ether (82%, mp 83–84 °C); ^{1}H NMR gave singlets at δ 1.08 (6 H), 1.83 (3 H), 2.23 (3 H), 2.33 (4 H), and a pair of doublets centered at 6.72 and 7.03 (4 H, J = 9.0 Hz); IR (chloroform) 5.95, 6.06, 6.20, and 6.25 μ.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.66; H, 8.25; O, 13.09. Found: C, 78.64; H, 8.22.

2-(*o*-Carbomethoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5h). Attempted preparation of **5h** from methyl *o*-hydroxybenzoate and epoxide **4** gave no reaction after 52 h (^{1}H NMR analysis).

2-(*m*-Carbomethoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5i) was prepared from methyl *m*-hydroxybenzoate and epoxide **4** and crystallized from ether-petroleum ether (90%, mp 75–76 °C); ^{1}H NMR gave singlets at δ 1.19 (6 H), 1.90 (3 H), 2.44 (4 H), 3.92 (3 H), and a multiplet at 7.1–7.8 (4 H); IR (chloroform) 5.73, 5.88, 6.00, and 6.21 μ.

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.81; H, 7.07.

2-(*p*-Carbomethoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5j) was prepared from methyl *p*-hydroxybenzoate and epoxide **4** and crystallized from ether–petroleum ether (87%, mp 70.5–72.0 °C); ^{1}H NMR gave singlets at δ 1.17 (6 H), 1.88 (3 H), 2.45 (4 H), 3.89 (3 H), and a pair of doublets centered at 6.86 and 7.97 (4 H, J = 9.0 Hz); IR (chloroform) 5.83, 5.93, 6.02, and 6.24 μ.

2-(*m*-Carboxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5k). A solution of **5i** (425 mg, 1.48 mmol) in methanol (10 mL) and 6 N sodium hydroxide (500 μL) was stirred at 25 °C for 4 h. Crystallization from methylene chloride–petroleum ether gave **5k** (396 mg, 95%, mp 191–192 °C); ^{1}H NMR gave singlets at δ 1.18 (6 H), 1.93 (3 H), 2.50 (4 H), and a multiplet at 7.10–7.95 (4 H); IR (chloroform) 3.0–4.0, 5.91, 6.02, and 6.23 μ.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.01; H, 6.58.

2-(*p*-Acetylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5l) was prepared from *p*-hydroxyacetophenone and epoxide **4**, column chromatographed (no. 3 silica gel, 70:30 petroleum ether–methylene chloride solvent) and crystallized from ether–petroleum ether (88%, mp 77.0–78.5 °C); ^{1}H NMR gave singlets at δ 1.17 (6 H), 1.89 (3 H), 2.45 (4 H), 2.52 (3 H), and a pair of doublets centered at 6.89 and 7.91 (4 H, J = 8.5 Hz); IR (chloroform) 5.95, 6.04, 6.28, and 6.33 μ.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.92; H, 7.44.

2,2,4-Trimethyl-2,3-dihydrodibenz[*b,f*]oxepin-10(1H)-one (6). Attempted preparation of 2-(*o*-acetylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (**5m**) from *o*-hydroxyacetophenone and epoxide **4** gave, after column chromatography (silica gel, 50:50 methylene chloride–petroleum ether solvent) and crystallization from ether–petroleum ether, **6** as pale yellow crystals (78%, mp 103–104 °C); ^{1}H NMR gave singlets at δ 1.28 (6 H), 2.25 and 2.30 (5 H combined), 6.46 (1 H, broad) and multiplets at 2.61 (2 H) and 7.06–7.57 (4 H); IR (chloroform) 6.03, 6.28, and 6.38 μ; electron impact mass spectrum *m/e* 254.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.22; H, 7.09.

2-(2-Methoxy-5-cyanophenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5n) was prepared from 2-methoxy-5-cyanophenol and epoxide **4** and crystallized from ether (74%, mp 155–156 °C); ^{1}H NMR gave singlets at δ 1.13 (6 H), 1.90 (3 H), 2.40 and 2.43 (4 H, unresolved), 3.95 (3 H), and a multiplet at 6.7–7.4 (3 H); IR (chloroform) 4.49, 5.95, 6.05, 6.22, 6.32, 6.60, and 7.90 μ.

2-(2-Methoxy-5-dithiolanophenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5o) was prepared from isovanillin ethylenedithioacetal and epoxide **4** and crystallized from methylene chloride–petroleum ether (62%, mp 139–140 °C); ^{1}H NMR gave singlets at δ 1.15 (6 H), 1.90 (3 H), 2.40 (4 H, broad), 3.35 (4 H, broad), 3.91 (3 H), 5.55 (1 H), and a multiplet at 6.70–7.35 (3 H); IR (chloroform) 5.95, 6.08, 6.24, and 6.30 μ; electron impact mass spectrum *m/e* 364.

Anal. Calcd for $C_{19}H_{24}O_3S_2$: C, 62.60; H, 6.64; O, 13.17; S, 17.59. Found: C, 62.52; H, 6.61; S, 17.48.

2-(2-Methoxy-5-carbomethoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5p) was prepared from 2-methoxy-5-carbomethoxyphenol and epoxide **4** and crystallized from ether–petroleum ether (90%, mp 124–125 °C); ^{1}H NMR gave singlets at δ 1.03 (6 H), 1.95 (3 H), 2.47 (4 H), 3.86 (3 H), 3.99 (3 H), and multiplets centered at 6.95 (1 H, doublet, J = 8.5 Hz), 7.25 (1 H, doublet, J = 2.0 Hz), and 7.70 (1 H, doublet of doublets, J = 8.5 and 2.0 Hz); IR (chloroform) 5.85, 5.96, 6.09, 6.21, and 6.31 μ.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.97; H, 7.00.

2-(*m*-*N,N*-Dimethylaminophenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5q) was prepared from *m*-*N,N*-dimethylaminophenol and epoxide **4**, column chromatographed (no. 3 silica gel, chloroform solvent), and crystallized from ether–petroleum ether (50%, mp 102–103 °C); ^{1}H NMR gave singlets at δ 1.15 (6 H), 1.87 (3 H), 2.37 (4 H), 2.92 (6 H), and a multiplet at 6.2–7.1 (3 H); IR (chloroform) 5.92, 6.03, and 6.20 μ.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.68; H, 8.45.

2-(2-Chloro-5-methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5r) was prepared from 2-chloro-5-methylphenol and epoxide **4** and crystallized from ether–petroleum ether (85%, mp 95.0–96.5 °C); ^{1}H NMR gave singlets at δ 1.16 (6 H), 1.86 (3 H), 2.22 (3 H), 2.41 (4 H), and multiplets centered at 6.36 (1 H, doublet, J = 2 Hz), 6.66 (1 H, doublet of doublets, J = 2 and 8 Hz), and 7.20 (1 H, doublet, J = 8 Hz); IR (chloroform) 5.93, 6.06, 6.21, and 6.30 μ.

Anal. Calcd for $C_{16}H_{19}ClO_2$: C, 68.93; H, 6.87. Found: C, 68.92; H, 6.74.

2-(2-*tert*-Butyl-5-methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5s) was prepared from 2-*tert*-butyl-5-methylphenol and epoxide **4** and crystallized from ether–petroleum ether (72%, mp 85–87 °C); ^{1}H NMR gave singlets at δ 1.33 (3 H), 1.47 (9 H), 1.85 (3 H), 2.18 (3 H), 2.38 (4 H, broad), 6.24 (1 H, broad), and multiplets centered at 6.66 (1 H, broadened doublet, J = 8 Hz), and 7.16 (1 H, doublet, J = 8 Hz); IR (chloroform) 5.92, 6.06, 6.18, and 6.30 μ.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.91; H, 9.42.

2-(3-Chloro-5-methoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5t) was prepared from 3-chloro-5-methoxyphenol and epoxide **4** and crystallized from ether–petroleum ether (97%, mp 83–85 °C); ^{1}H NMR gave singlets at δ 1.11 (6 H), 1.86 (3 H), 2.39 (4 H), 3.72 (3 H), and a multiplet at 6.1–6.6 (3 H).

2-(4-Chloro-3-methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5u) was prepared from 4-chloro-3-methylphenol and epoxide **4** and crystallized from ether–petroleum ether (90%, mp 82–84 °C); ^{1}H NMR gave singlets at δ 1.15 (6 H), 1.88 (3 H), 2.30 (3 H), 2.40 (4 H), and multiplets centered at 6.56 (1 H, doublet of doublets, J = 2.5 and 8.5 Hz), 6.89 (1 H, triplet, J = 2.5 Hz), and 7.34 (1 H, doublet, J = 8.5 Hz); IR (chloroform) 5.93, 6.05, 6.17, and 6.28 μ.

10-Methyl-1-phenoxy-$\Delta^{1(9)}$-octalone-2 (10a) was prepared from phenol and the epoxide of 10-methyl-$\Delta^{1(9)}$-octalone-2 (70:30 mixture of two diastereoisomers) and crystallized from ether–petroleum ether (93%, mp 71.0–72.5 °C); ^{1}H NMR gave a singlet at δ 1.37 (3 H) and a multiplet at 6.7–7.4 (5 H); IR (Nujol) 5.96, 6.18, 6.28, 6.30, 13.35, and 14.54 μ.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.72; H, 7.85.

Phenoxymethyl Vinyl Ketone (12a). Lithium phenoxyacetate was prepared by addition of phenoxyacetic acid[18] to lithium carbonate in aqueous solution, after which solvent was evaporated and the residue was dried in a vacuum oven at 70 °C for 24 h. To a vigorously stirred suspension of lithium phenoxyacetate (3.16 g, 20 mmol) in dimethoxyethane (DME, 20 mmol) was added vinylmagnesium bromide (20 mL of a 1.4 M solution in THF, 1.4 equiv) dropwise during 90 min in a nitrogen atmosphere. After stirring for 24 h at room temperature, the reaction mixture was carefully siphoned into cold 1 N hydrochloric

acid (50 mL) and the resulting suspension was washed with ether (1 × 50 mL, 2 × 25 mL). The organic solution was washed with water (2 × 25 mL), 1 N sodium carbonate (3 × 25 mL), and water (4 × 25 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent gave phenoxymethyl vinyl ketone (2.59 g, 80%, oil) of good purity (^{1}H NMR analysis). Distillation resulted in significant decomposition, e.g., distillation of 10.4 g gave 4.0 g of pure **12a** (bp 63–65 °C at 0.15 mm), which polymerized on standing at room temperature and generally was used directly or stored in benzene solution in a nitrogen atmosphere at 0 °C; ^{1}H NMR δ 4.70 (2 H, singlet), 5.60–6.65 (3 H, multiplet), and 6.7–7.5 (5 H, multiplet); IR (neat) 5.88 and 6.25 μ.

10-Carboethoxy-1-phenoxy-$\Delta^{1(9)}$-octalone-2 (10b). To a solution of ethyl 2-cyclohexanonecarboxylate (19 g, 0.11 mol) and crude **12a** (17 g) in dry benzene (210 mL)–heptane (210 mL) was added fused zinc chloride (1.32 g, 10 mmol) in a nitrogen atmosphere. After stirring at room temperature for 1 h, the mixture was heated at reflux temperature for 10 h. The resulting light orange solution was washed with 1 N sodium hydroxide (3 × 70 mL) and saturated sodium chloride solution (2 × 100 mL). Evaporation of solvent and distillation at 0.03 mm gave recovered ethyl 2-cyclohexanonecarboxylate (8.5 g). ^{1}H NMR analysis of the residue indicated that nearly pure Michael adduct was present (18.5 g, 50%; 91% based on recovered ethyl 2-cyclohexanonecarboxylate); ^{1}H NMR gave resonances at δ 1.21 (3 H, triplet, J = 7 Hz), 1.3–2.8 (12 H, multiplet), 4.20 (2 H, quartet, J = 7 Hz), 4.50 (2 H, singlet), and 6.7–7.4 (5 H, multiplet).

A solution of the Michael adduct thus obtained (3.32 g, 10 mmol) in THF (70 mL) was added to a stirred suspension of KH (1 equiv, free of oil) in THF (30 mL) in a nitrogen atmosphere at 5 °C. After stirring for an additional 10 min, the cooling bath was removed, HMPA (7.0 mL) was added, and the resulting solution was heated at reflux for 17 h, after which time THF was removed at reduced pressure. Ether (75 mL)–petroleum ether (75 mL) was added to the residue and the solution was washed with water (4 × 100 mL), dried over anhydrous magnesium sulfate, and distilled to give **10b** (2.95 g, 94%, bp 177–179 °C at 0.03 mm); crystallization from methanol–water gave analytically pure **10b** (mp 62–64 °C); ^{1}H NMR gave resonances at δ 1.32 (3 H, triplet, J = 7.0 Hz), 1.4–2.7 (11 H, multiplet), 3.0 (1 H, broad doublet, $J \sim 14$ Hz), 4.29 (2 H, quartet, J = 7 Hz), and 6.6–7.4 (5 H, multiplet); IR (neat) 5.80, 5.94, and 6.27 μ; electron impact mass spectrum m/e 314.

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.55; H, 7.07.

2-Methoxy-5-cyanophenoxymethyl Vinyl Ketone (12b). The required 2-methoxy-5-cyanophenoxyacetic acid was prepared by heating a solution of 2-methoxy-5-cyanophenol (2.98 g, 20 mmol), chloroacetic acid (2.00 g, 21.2 mmol), and sodium hydroxide (1.72 g, 43 mmol) in water (15 mL) to reflux for 13 h. The resulting, cooled solution was acidified (6 N hydrochloric acid to pH ~1) and filtered. The filtrate was washed with ethyl acetate (2 × 20 mL), the organic layer was combined with the solid material, and additional ethyl acetate (200 mL) was added. The resulting solution was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of solvent and crystallization from ethyl acetate–benzene gave 2-methoxy-5-cyanophenoxyacetic acid (3.00 g, 73%, mp 160.5–161.5 °C); a second crop of crystalline material was collected (total 3.46 g, 84%, mp 156–160 °C); ^{1}H NMR (acetone-d_6) δ 3.95 (3 H, singlet), 4.83 (2 H, singlet), and 7.0–7.5 (4 H, multiplet); IR (Nujol) 3.00–3.60, 4.51, 5.82, 6.25, and 6.35 μ.

Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38. Found: C, 57.90; H, 4.37.

2-Methoxy-5-cyanophenoxymethyl vinyl ketone (**12b**) was prepared from 2-methoxy-5-cyanophenoxyacetic acid by the procedure described for preparation of **12a** (42%, relatively unstable oil): ^{1}H NMR δ 3.95 (3 H, singlet), 4.87 (2 H, singlet), 5.7–6.7 (3 H, multiplet), and 6.7–7.8 (3 H, multiplet); IR (neat) 4.50, 5.90, 6.25, and 6.32 μ.

1,2,3,4,6,7,8,9-Octahydro-2-methyl-5-(2-methoxy-5-cyanophenoxy)-6-oxo-9-carbethoxyisoquinoline (15). Annelation Route. To a stirred solution of **13** (11.8 mL, 12.9 g, 70 mmol)[12] in methanol (70 mL) containing potassium hydroxide (3.50 mmol, 5 mol %) was added a solution of **12a** in benzene (1.0 M, 70 mL, 70 mmol) in a nitrogen atmosphere. After 24 h, solvent was evaporated and benzene (500 mL) was added to the residue. The resulting solution was washed with water (1 × 100 mL) and saturated sodium chloride solution (1 × 100 mL), dried over anhydrous magnesium sulfate, and evaporated to give a pale yellow oil, which was used without further purification.

A solution of the crude Michael adduct (7.94 g, 20 mmol) and pyrrolidine (4.2 mL, 50 mmol) in benzene (12 mL) was heated to reflux in a nitrogen atmosphere in a reactor equipped with a water separator for 24 h. After cooling, 6 N hydrochloric acid (50 mL) was added and the mixture was stirred at room temperature for 90 min. After separation of layers, the aqueous layer was washed with methylene chloride (20 mL), made basic (pH ~9) with solid sodium carbonate, and extracted with methylene chloride (3 × 20 mL). The organic solution was washed with water (20 mL) and saturated sodium chloride (20 mL) and dried over anhydrous magnesium sulfate. Removal of solvent, filtration chromatography (no. 3 silica gel, methylene chloride solvent), and crystallization from methylene chloride–petroleum ether gave **15** (3.26 g, 43% from **13**, mp 171–172 °C): ^{1}H NMR δ 1.37 (3 H, triplet, J = 7 Hz), 2.28 (3 H, singlet), 1.70–3.62 (10 H, multiplet), 3.98 (3 H, singlet), 4.33 (2 H, quartet, J = 7 Hz), and 6.82–7.42 (3 H, multiplet); IR (chloroform) 4.50, 5.80, 5.93, 6.10, 6.22, and 6.32 μ; chemical ionization mass spectrum m/e 385 (100%); electron impact m/e 384 (56%).

Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.65; H, 6.30; N, 7.28.

Decahydro-2-methyl-5,10-epoxy-6-oxo-9-carbethoxyisoquinoline (14a). Hydrogen peroxide (30%, 6 mL, 63 mmol) was added to a stirred solution of 1,2,3,4,6,7,8,9-octahydro-2-methyl-6-oxo-9-carbethoxyisoquinoline (**14**,[12] mp 171–172 °C, 4.74 g, 20 mmol) in 1 N aqueous sodium hydroxide (10 mL) and methanol (20 mL) at 0–5 °C during 30 min. Stirring was continued at 0–10 °C for 4 h and at room temperature for 1 h. Saturated sodium chloride (15 mL) was added along with excess solid sodium chloride and continuous extraction with ether was performed for 16 h. The ether solution was washed with saturated sodium chloride (10 mL) and dried over anhydrous magnesium sulfate. Removal of solvent and filtration chromatography (4 g, no. 3 silica gel, methylene chloride solvent) gave analytically pure **14a** (4.02 g, 80%, mp 88–90 °C) on evaporation of methylene chloride: ^{1}H NMR δ 1.23 (3 H, triplet, J = 7 Hz), 2.32 (3 H, singlet), 1.40–3.50 (10 H, multiplet), 3.28 (1 H, singlet), and 4.22 (2 H, quartet, J = 7 Hz); IR (Nujol) 5.78, 5.86, and 8.00 μ.

Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56. Found: C, 61.77; H, 7.54.

1,2,3,4,6,7,8,9-Octahydro-2-methyl-5-(2-methoxy-5-cyanophenoxy)-6-oxo-9-carbethoxyisoquinoline (15). Epoxy Ketone Route. 15 was prepared from 2-methoxy-5-cyanophenol and epoxide **14a** as described for preparation of **5a** (15-g scale, 90%).

Irradiation of 2-Phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one (5a). General Photochemical Procedure for Dihydrofuran Formation. A solution of **5a** (20 g, 0.087 mol, 0.043 M) in benzene–methanol–acetic acid (1:1:1, 2000 mL) was purged with argon for 30 min prior to and during irradiation with Pyrex-filtered light. After 22 h, reaction was complete (VPC analysis as noted in preparation of **5a**; retention time **17a**, 19 min (95%); **19**, 30 min). Solvent was evaporated and to the residue was added ether (200 mL). The ether solution was washed with 1 N sodium hydroxide (3 × 50 mL) and saturated sodium chloride (2 × 50 mL), and dried over anhydrous magnesium sulfate. Evaporation of solvent gave pure **17a** (^{1}H NMR and VPC analysis), which crystallized on standing (17.6 g, 88%). Recrystallization from ether–petroleum ether gave analytically pure **17a** (15.9 g, 80%, mp 85–87 °C); ^{1}H NMR gave singlets at δ 0.60 (3 H), 1.10 (3 H), 1.40 (3 H), 4.52 (1 H), and multiplets at 2.0–2.4 (4 H), and 6.7–7.2 (4 H); IR (chloroform) 5.79, 6.25, 6.80, 8.42, 9.65, 11.92, and 13.20 μ; electron impact mass spectrum m/e 230.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.36; H, 7.92.

The basic washes were combined, acidified with hydrochloric acid (pH ~2), and extracted with ether (2 × 50 mL). The organic solution was washed with saturated sodium chloride solution (25 mL), dried over anhydrous magnesium sulfate, and evaporated to give an oil (2.54 g, 12%), of which **17a** was the major component (VPC analysis). Crystallization from ether–petroleum ether gave **19** (0.34 g, 1.7%, mp 172–175 °C); ^{1}H NMR gave singlets at δ 1.11 (6 H), 1.83 (3 H), 2.42 (4 H), 5.8 (1 H, broadened, disappears on addition of deuterium oxide), and a multiplet at 6.8–7.4 (4 H); IR (chloroform) 3.00, 6.03, and 6.24 μ; electron impact mass spectrum m/e 230.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.14; H, 7.94.

Irradiation of **5a** (53 mg) in degassed benzene solution (3.2 mL) in a bath cooled to 0 °C for 2 h, evaporation of solvent at room temperature, and ^{1}H NMR analysis indicated a complex mixture of

products, from which **17a** was absent. A singlet at δ 4.90 suggested the presence of **18** (~30%); treatment of the crude photoreaction mixture with sodium carbonate in benzene–methanol (1:1) resulted in the disappearance of the NMR signal at δ 4.9 and the appearance of the singlet at 4.52 due to the C(2) hydrogen in **17a** (30%).

Irradiation of dihydrofuran 17a was performed on a 50-mg scale in degassed[17] benzene–methanol–acetic acid (3.2 mL, 1:1:1), 24-h irradiation. VPC and ^{1}H NMR analysis indicated that **17a** (28%), phenol **19** (57%), and minor components (15%) were present.

Irradiation of 2-(*o*-methoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5b) was performed on a 50-mg scale, 8-h irradiation. ^{1}H NMR analysis indicated consumption of **5b** and formation of **17b** (30%); e.g., new resolved singlets at δ 0.60 (3 H), 1.39 (3 H), and 4.54 (1 H).

Irradiation of 2-(*m*-methoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5c) was performed on a 100-mg scale in 6.4 mL of benzene–methanol–acetic acid, 8-h irradiation time. VPC analysis indicated formation of **17c** (92%) and a secondary photoproduct analogous to rearranged phenol **19** (5%). The photolysis solution was evaporated and ether (25 mL) was added to the residue. The ether solution was washed with 1 N sodium hydroxide (2 × 10 mL) and saturated sodium chloride (1 × 10 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent gave pure **17c** (VPC and ^{1}H NMR analysis, 90 mg, 90%, oil); ^{1}H NMR gave singlets at δ 0.68 (3 H), 1.08 (3 H), 1.44 (3 H), 2.29 (2 H), 3.82 (3 H), 4.42 (1 H), doublets centered at 1.78 and 2.72 (2 H, J = 14.5 Hz), and a characteristic pattern for 4-substituted benzodihydrofurans in the aromatic region; e.g., broadened doublets for protons at C(5) and C(7) at 6.42 and 6.58 (2 H, J = 8.0 Hz) and a sharp triplet for the proton at C(6) at 7.10 (1 H, J = 8.0 Hz); IR (neat) 5.78, 6.24, 12.8, and 13.6 μ.

The basic washes were combined and treated as described for isolation of **19.** In this way a rearranged phenol analogous to **19** was obtained (5 mg, 5%, oil); ^{1}H NMR gave singlets at δ 1.10 (6 H). 1.85 (3 H), 2.43 (4 H), 3.78 (3 H), a multiplet at 6.3–7.3 (3 H), and a broad singlet at 8.38 (1 H); IR (neat) 3.00, 3.40, 5.88, 6.10, 6.22, and 6.28 μ.

Irradiation of 2-(*p*-methoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5e) was performed on a 50-mg scale; 3-h irradiation time. VPC analysis indicated formation of **17e** (91%). Preparative-scale irradiation (0.75 g in 60 mL of solvent), evaporation of solvent, and crystallization from ether–petroleum ether gave **17e** (0.60 g, 80%, mp 71–73 °C); ^{1}H NMR gave singlets at δ 0.58 (3 H), 1.19 (3 H), 1.39 (3 H), 2.30 (3 H), 4.52 (1 H), and multiplets at 2.48–1.66 (4 H) and 6.7–7.1 (3 H).

Irradiation of 2-(*m*-methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5f) was performed on a 50-mg scale; 2.5-h irradiation time. ^{1}H NMR and VPC analysis indicated a quantitative conversion to a 75:25 mixture of the 4-methylbenzodihydrofuran and the 6-methylbenzodihydrofuran, respectively; selected proton NMR data δ 4.40 (0.75 H), 4.48 (0.25 H).

Irradiation of 2-(*p*-methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5g) was performed on a 1.0-g scale. Crystallization from ether–petroleum ether gave **17g** (0.80 g, mp 72.0–73.5 °C); ^{1}H NMR gave singlets at δ 0.60 (3 H), 1.10 (3 H), 1.38 (3 H), 2.27 (3 H), 4.51 (1 H), and multiplets at 1.56–2.50 (4 H) and 6.80–7.00 (3 H).

Irradiation of 2-(*m*-carbomethoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5i) was performed on a 50-mg scale in benzene–methanol (1:1, 3 mL); 2-h irradiation time. ^{1}H NMR and VPC analysis indicated a quantitative conversion to a 65:35 mixture of the 4-carbomethoxybenzodihydrofuran and the 6-carbomethoxybenzodihydrofuran, respectively; selected NMR data δ 4.48 (0.65 H), 4.56 (0.35 H).

Irradiation of 2-(*p*-carbomethoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5j) was performed on a 50-mg scale in benzene–methanol (1:1, 3 mL); 2-h irradiation time. Evaporation of solvent and ^{1}H NMR analysis indicated a quantitative yield of **17j** (oil); ^{1}H NMR singlets at δ 0.59 (3 H), 1.13 (3 H), 1.44 (3 H), 3.92 (3 H), 4.65 (1 H), a multiplet at 1.8–2.4 (4 H), and multiplets centered at 6.96 (1 H, doublet, J = 8.0 Hz), 7.82 (1 H, doublet, J = 1.5 Hz), and 7.90 (1 H, doublet of doublets, J = 8.0 and 1.5 Hz); IR (chloroform) 5.84, 5.89, and 6.21 μ.

Irradiation of 2-(*m*-carboxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5k) was performed on a 50-mg scale in benzene–methanol (1:1, 3 mL); 2-h irradiation time. ^{1}H NMR analysis indicated a quantitative conversion to a 63:37 mixture of the 4-carboxybenzodihydrofuran and the 6-carboxybenzodihydrofuran, respectively; selected ^{1}H NMR data δ 4.54 (0.63 H), 4.62 (0.37 H).

Irradiation of 2-(*p*-acetylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5l) was performed on a 50-mg scale; 2-h irradiation time. ^{1}H NMR analysis indicated a quantitative yield of **17l**; e.g., δ 0.55 (3 H, singlet), 1.12 (3 H, singlet), 1.41 (3 H, singlet), 1.86–2.60 (7 H, multiplet with partially resolved 3 H singlet at 2.55), 4.68 (1 H, singlet), 7.01 (1 H, doublet, J = 8.0 Hz), and 7.7–8.0 (2 H, multiplet); IR (neat) 5.76, 5.95, and 6.21 μ.

Irradiation of 2-(2-methoxy-5-cyanophenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5n) was performed on a 100-mg scale. Crystallization from methylene chloride–ether gave **17n** (87 mg, 87%); ^{1}H NMR gave singlets at 0.70 (3 H), 1.15 (3 H), 1.52 (3 H), 3.96 (3 H), 4.65 (1 H), and a multiplet at 1.78–3.06 (4 H) and an AB quartet centered at 6.80 and 7.20 (2 H, J_{AB} = 9.0 Hz).

Irradiation of 2-(2-methoxy-5-dithiolanophenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5o) was performed on a 50-mg scale; 4-h irradiation time. VPC analysis indicated formation of **17o** (58%). Preparative-scale irradiation (0.50 g in 120 mL of solvent), evaporation of solvent and preparative thick layer chromatography (silica gel) gave pure **17o** (200 mg, 40%, oil); ^{1}H NMR gave singlets at δ 0.83 (3 H), 1.12 (3 H), 1.60 (3 H), 3.90 (3 H), 4.43 (1 H), 5.90 (1 H), and multiplets at 1.72–2.45 (4 H), 3.16–3.72 (4 H), and an AB quartet centered at 6.80 and 7.41 (2 H, J_{AB} = 9.0 Hz).

Irradiation of 2-(2-methoxy-5-carbomethoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5p) was performed on a 2.00-g scale in benzene–methanol (1:1, 300 mL); 3-h irradiation time. Evaporation of solvent and crystallization from ether–petroleum ether gave **17p** (1.91 g, 96%, mp 146.0–147.5 °C); ^{1}H NMR gave singlets at δ 0.78 (3 H), 1.07 (3 H), 1.63 (3 H), 2.30 (2 H), 3.88 (3 H), 3.98 (3 H), 4.55 (1 H), doublets centered at 1.94 (1 H, J = 15 Hz), 2.81 (1 H, J = 15 Hz), and an AB quartet centered at 6.79 and 7.50 (2 H, J_{AB} = 8.5 Hz); IR (chloroform) 5.83, 5.88, and 6.21 μ.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.84; H, 6.94.

Irradiation of 2-(*m*-*N*,*N*-dimethylaminophenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5q) was performed on a 50-mg scale in (1) benzene–methanol solution and (2) benzene–methanol saturated with sodium carbonate. In both cases, no reaction was observed after 5-h irradiation time. In benzene–methanol, little polymerization occurred up to 21 h, extensive polymerization after 72 h, and after 116 h all **5q** was consumed. Under no conditions could the presence of **17q** be detected.

Irradiation of 2-(2-Chloro-5-methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5r) was performed on a 1.5-g scale in benzene–methanol (1:1, 270 mL); 3.5-h irradiation time. Evaporation of solvent and crystallization followed by recrystallization from petroleum ether gave **17r** (1.28 g, 83%, mp 134–136 °C); ^{1}H NMR gave singlets at δ 0.72 (3 H), 1.08 (3 H), 1.45 (3 H), 2.31 (5 H), 4.47 (1 H), doublets centered at 1.86 (1 H, J = 14 Hz), 2.44 (1 H, J = 14 Hz), and an AB quartet centered at 6.56 and 6.96 (2 H, J_{AB} = 8.5 Hz); IR (chloroform) 5.76 and 6.13 μ.

Anal. Calcd for $C_{16}H_{19}ClO_2$: C, 68.93; H, 6.87. Found: C, 69.06; H, 6.93.

Irradiation of 2-(2-*tert*-butyl-5-methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5s) was performed on a 1.3-g scale in benzene–methanol (1:1, 270 mL); 1.5-h irradiation time. Evaporation of solvent and crystallization followed by recrystallization from petroleum ether gave **17s** (1.10 g, 85%, mp 84–86 °C); ^{1}H NMR gave singlets at δ 0.70 (3 H), 1.03 (3 H), 1.37 (9 H), 1.42 (3 H), 1.91–2.50 (7 H, partially resolved 3 H singlet and multiplet), 4.28 (1 H), and an AB quartet centered at 6.49 and 6.90 (2 H, J_{AB} = 8.5 Hz); IR (chloroform) 5.83 μ.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.91; H, 9.42.

Irradiation of 2-(3-chloro-5-methoxyphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5t) was performed on a 53-mg scale in (1) benzene–methanol solution and (2) benzene–methanol–acetic acid. In both cases ^{1}H NMR analysis indicated a quantitative conversion to a 58:42 mixture of the two possible dihydrofurans. In benzene or methylene chloride solution, the photoreaction was not as clean, but the ratio of dihydrofurans formed was the same as in protic solvents; selected ^{1}H NMR data δ 4.57 (0.58 H), 4.61 (0.42 H).

Irradiation of 2-(4-chloro-3-methylphenoxy)-3,5,5-trimethyl-2-cyclohexen-1-one (5u) was performed on a 55-mg scale in benzene–methanol solution: 1.5-h irradiation time. ^{1}H NMR analysis indicated a quantitative conversion to a 70:39 mixture of the 4-methyl-5-chlo-

robenzodihydrofuran and the 6-methyl-5-chlorobenzodihydrofuran, respectively; selected ^{1}H NMR data δ 4.43 (0.70 H), 4.51 (0.30 H).

Irradiation of 10-methyl-1-phenoxy-$\Delta^{1(9)}$-octalone-2 (10a) was performed on a 71-mg scale in benzene (3.2 mL) solution saturated with *p*-toluenesulfonic acid; 9.5-h irradiation time. ^{1}H NMR and VPC analysis indicated formation of dihydrofuran **21** (90%) and diketone **22a** (4–5%); VPC (3 ft × $^1/_8$ in. glass column filled with 5% Dexsil on Gas Chrom Q, 100/120 mesh size at 230 °C; retention time **22a**, 2 min; **21**, 14 min). Electron impact mass spectral analysis gave for **22a** *m/e* 180 (100%) and **21** *m/e* 256 (5%), 85 (100%). Preparative scale irradiation of **10a** (9.35 g) in benzene (300 mL) saturated with *p*-toluenesulfonic acid while purged with argon was monitored by VPC analysis; after 8 h, <2% **10a** remained. The benzene solution was washed with 1 N NaOH (3 × 50 mL) and water (5 × 60 mL), dried over anhydrous magnesium sulfate, and evaporated to give **21** (8.95 g, 95%, oil); ^{1}H NMR for **21** gave singlets at δ 0.92 (3 H), 4.43 (1 H), and multiplets at 1.3–3.0 (12 H) and 6.6–7.4 (4 H). Repetitive NMR integration in the region δ 4.5–6.0 on a concentrated sample of **21** thus obtained indicated that had the isomer of **21**, with a *trans*-decalone ring fusion, formed in the photoreaction of **10a**, then it was present in <1% yield.

Irradiation of 1,2,3,4,6,7,8,9-Octahydro-2-methyl-5-(2-methoxy-5-cyanophenoxy)-6-oxo-9-carbethoxylsoquinoline (15) in Benzene–Methanol. A solution of **15** (1.00 g, 2.60 mmol, 0.037 M) in benzene (35 mL)–methanol (35 mL) was irradiated for 3.5 h, after which TLC analysis revealed that **15** had been consumed. Removal of solvent and ^{1}H NMR analysis indicated a 60:40 mixture of **24** and **25a**, respectively. Column chromatography (50 g of silicia gel; gradient elution with methylene chloride to ether (20%)–methylene chloride) gave *trans*-dihydrofuran **24** (310 mg, 31%, mp 145–147 °C); ^{1}H NMR δ 1.18 (3 H, triplet, J = 7 Hz), 2.44 (3 H, singlet), 1.50–3.30 (9 H, multiplet), 3.82–4.02 (1 H, multiplet), 3.94 (3 H, singlet), 4.18 (2 H, quartet, J = 7 Hz), 5.22 (1 H, singlet), and 6.84, 7.28 (2 H, AB quartet, J_{AB} = 9 Hz); IR (KBr) 4.50, 5.75, 5.82, 6.29, and 6.38 μ; chemical ionization mass spectrum *m/e* 385 (100%).

Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29. Found: C, 65.57; H, 6.17.

Continued elution gave *cis*-dihydrofuran **25a** (280 mg, 28%, mp 163–165 °C): ^{1}H NMR δ 1.11 (3 H, triplet, J = 7 Hz), 2.13 (3 H, singlet), 1.60–3.70 (10 H, multiplet), 3.95 (3 H, singlet), 4.12 (2 H, quartet, J = 7 Hz), 4.55 (1 H, singlet), and 6.82, 7.20 (2 H, AB quartet, J_{AB} = 9 Hz); IR (KBr) 4.50, 5.80, 5.88, 6.21, and 6.37 μ; chemical ionization mass spectrum *m/e* 385 (100%).

Anal. Found: C, 65.66; H, 6.22.

Irradiation of 15 in Benzene–Methanol Saturated with Sodium Carbonate. A solution of **15** (400 mg, 1.04 mmol, 0.052 M) in benzene (10 mL)–methanol (10 mL) saturated with sodium carbonate was irradiated for 3 h. Removal of solvent, filtration chromatography (5 g of silica gel, methylene chloride solvent), and crystallization from methylene chloride–ether–petroleum ether gave *cis*-dihydrofuran **25a** (352 mg, 88%).

Irradiation of 15 in Benzene. A solution of **15** (14.0 g, 36.5 mmol, 0.12 M) in benzene (300 mL) was irradiated for 3 h. Removal of solvent gave crystalline **24** (14.0 g, 100%), sufficiently pure for further synthetic operations.

Epimerization of 24. A solution of *trans*-dihydrofuran **24** (1.00 g, 2.60 mmol) in benzene (10 mL)–methanol (10 mL) saturated with sodium carbonate was stirred in a nitrogen atmosphere for 24 h. Removal of solvent, filtration chromatography (Celite, benzene solvent), and crystallization gave *cis*-dihydrofuran **25a** (874 mg, 87%).

Irradiation of 15 in benzene–methanol-d_1 was performed on a 50-mg scale in (1) benzene–methanol (1:1, 3 mL) and (2) benzene–methanol-d_1 (1:1, 3 mL); 3-h parallel irradiation time. Removal of solvent at reduced pressure (room temperature) and ^{1}H NMR integration of the regions δ 5.22:4.55:6.9–7.2 gave for (1) 0.78:1.00:4.22 and (2) 0.02:1.00:4.05.

Irradiation of 24 and 25a in benzene–methanol-d_1 was performed on a 59-mg scale with (1) **24** and (2) **25a** in benzene–methanol-d_1 (1:1, 3 mL); 3-h irradiation time. ^{1}H NMR analysis indicated that while **24** was completely stable to irradiation, **25a** experienced complete deuterium incorporation at C(5).

Irradiation studies with 10-carboethoxy-1-phenoxy-$\Delta^{1(9)}$-octalone-2 (10b) were performed on a 52-mg scale in benzene–methanol–acetic acid (1:1:1, 3.2 mL); 10-h irradiation time. Benzene (75 mL) was added and the solution was washed with 1 N sodium bicarbonate, dried over anhydrous magnesium sulfate, and evaporated to give a nearly colorless oil (50 mg). ^{1}H NMR analysis indicated that *trans*-dihydrofuran **26** (29%), *cis*-dihydrofuran **27** (35%), and diketone **22b** (35%) were present. Benzene (75 mL) was added to the crude photoreaction and the resulting solution was washed with 1 N sodium hydroxide (2 × 20 mL) and saturated sodium chloride (2 × 20 mL), dried over anhydrous magnesium sulfate, and evaporated to give a clean mixture of **26** and **27**.

The sodium hydroxide layer was acidified (pH <2) with concentrated hydrochloric acid and was extracted with benzene (3 × 30 mL). The benzene solution was dried over anhydrous magnesium sulfate and evaporated to give diketone **22b** (oil): ^{1}H NMR δ 1.26 (3 H, triplet, J = 7 Hz), 1.2–3.3 (12 H, multiplet), 4.22 (2 H, quartet, J = 7 Hz), and ~6.25 (1 H, singlet, disappears on addition of deuterium oxide); electron impact mass spectrum (inlet temperature 105 °C) *m/e* 239 (64%), 238 (33%), ratio 239:238 highly dependent on inlet temperature, 165 ($M^+ - 74$; $HCO_2CH_2CH_3$).

Irradiation of **10b** in benzene saturated with *p*-toluenesulfonic acid gave **26** (40%), **27** (3%), diketone **22b** (14%), and apparently polymeric material (^{1}H NMR analysis). Irradiation in pure benzene resulted in a good deal more polymer formation, **26** (30%), and **22b** (~8%). Irradiation of **10b** (183 mg) and benzophenone (56 mg) in benzene (9 mL) with a Uranyl glass filter for 6 h, evaporation of solvent and standing gave colorless crystals. Filtration collection with the aid of benzene gave benzpinacol (~10 mg, mp 183–185 °C, lit. mp 186–188 °C). Column chromatography (silica gel) gave **26** (122 mg, 67%, oil): ^{1}H NMR δ 1.04 (3 H, triplet, J = 7 Hz), 1.2–3.3 (12 H, multiplet), 4.10 (2 H, quartet, J = 7 Hz), 5.10 (1 H, doublet, J = 1.5 Hz), and 6.7–7.6 (4 H, multiplet).

Epimerization of 26. The procedure described for epimerization of **24** gave *cis*-dihydrofuran **27** (oil): ^{1}H NMR δ 0.99 (3 H, triplet, J = Hz), 1.2–3.0 (12 H, multiplet), 3.95 (2 H, quartet, J = 7 Hz), 4.43 (1 H, singlet), and 6.7–7.6 (4 H, multiplet).

Saponification of 24 and 26. Treatment of either **24** or **25** (~59 mg) in methanol (5 mL) solution with excess aqueous 1 N potassium hydroxide at room temperature for 2.5 h was followed by addition of water (50 mL) washing with benzene–ether (1:1, 2 × 50 mL), and acidification (pH ~1) with concentrated hydrochloric acid. The resulting aqueous solution was stirred at room temperature for 10 min and then was washed with ether–benzene (1:1, 2 × 50 mL). Evaporation of the organic layer and crystallization from ether gave analytically pure **28** (~45 mg, ~90%, mp 232–235 °C): ^{1}H NMR δ 1.2–2.9 (12 H, multiplet), 4.25 (singlet), 4.4 (broad singlet, disappears on addition of deuterium oxide), and 6.7–7.6 (4 H, multiplet); IR (Nujol) 2.89, 2.93, 5.71, 6.18, 6.26, 12.80, and 13.14 μ; electron impact mass spectrum *m/e* 286 (50%), 185 (100%).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.28: H, 6.34.

Reductive Cleavage of 24 and 26. Treatment of either **24** or **26** (~60 mg) in propionic acid (3 mL) with zinc dust (2.0 g) at reflux temperature for 10 h was followed by evaporation of solvent at reduced pressure. The residue was washed with ether (3 × 10 mL) and the resulting ether solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and evaporated to give lactone **29** (oil): ^{1}H NMR δ 1.0–3.0 (14 H, multiplet) and 6.7–7.5 (4 H, multiplet); IR (neat) 5.69 and 5.80 μ; chemical ionization mass spectrum *m/e* 271 (100%).

Reductive Cleavage of 17a. The procedure described for reductive cleavage of **24**, except that acetic acid was used and reaction time was 8 h, gave pure **31** (100%, ^{1}H NMR analysis); crystallization from petroleum ether gave analytically pure **31** (84%, mp 97–98 °C); ^{1}H NMR gave sharp singlets at δ 0.48 (3 H), 0.91 (3 H), 1.32 (3 H), and a broad singlet at 4.5 (1 H, disappears on addition of deuterium oxide); IR (neat) 2.90 and no absorption in the region 5–6 μ; chemical ionization mass spectrum *m/e* 233 (30%), $M^+ - 18$ (100%).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.41; H, 8.66.

Baeyer–Villiger Oxidation of 17a. A solution of dihydrofuran **17a** (2.30 g, 0.01 mol) and *m*-chloroperbenzoic acid (2.75 g of 85% peracid, 0.014 mol) in methylene chloride (23 mL) was stirred at room temperature for 20 h. The resulting thick white suspension was filtered through Celite which was then washed thoroughly with fresh solvent (2 × 25 mL). The combined methylene chloride solution was washed successively with 1 N sodium bisulfite (2 × 75 mL), 1 N sodium bicarbonate (3 × 75 mL), water (2 × 50 mL), and saturated sodium chloride solution (1 × 50 mL) and dried over anhydrous magnesium

sulfate. Evaporation of solvent and recrystallization from ether gave *cis*-3,3-dimethyl-4-[2-hydroxy-3-methyl-3-(2,3-dihydrobenzo[*b*]-furanyl)]butanoic acid ϵ-lactone (**32**, 2.38 g, 97%, mp 110–111 °C); ^{1}H NMR gave singlets at δ 0.91 (3 H), 1.20 (3 H), 1.40 (3 H), 2.41 (2 H), 5.96 (1 H), an AB quartet centered at 1.75 and 2.05 (2 H, J_{AB} = 15.0 Hz), and a multiplet at 6.71–7.36 (4 H); IR (chloroform) 5.70, 6.77, and 6.85 μ.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.36. Found: C, 73.12; H, 7.38.

Rearrangement–Cyclization of Lactone 32. To a stirred solution of lactone **32** (6.20 g, 0.025 mol) in methylene chloride (50 mL) at 0 °C was added titanium tetrachloride (7 mL, 0.063 mol). The deep purple solution was refluxed for 76 h, then cooled to 10 °C. Water (10 mL) was added slowly and the mixture was acidified with 1 N hydrochloric acid (25 mL) and extracted with ether (3 × 50 mL). The combined extracts were successively washed with 1 N hydrochloric acid (3 × 50 mL), 1 N sodium carbonate (3 × 25 mL), and water (3 × 25 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent gave pure 2-methyl-3,4-(2,2-dimethyl-4-oxobutano)benzo[*b*]furan (**34**, 5.40 g, 94%, mp 88–89 °C): ^{1}H NMR δ 1.11 (6 H, singlet), 2.42 (3 H, triplet, J = 1.0 Hz), 2.74 (2 H, broad singlet), 2.95 (2 H, singlet), 7.24 (1 H, doublet of doublets, J = 7.7 and 7.8 Hz), 7.57 (1 H, doublet of doublets, J = 7.8 and 1.2 Hz), and 7.91 (1 H, doublet of doublets, J = 7.8 and 1.2 Hz); IR (Nujol) 6.03 and 6.20 μ; electron impact mass spectrum *m/e* 228 (69%), 144 (100%).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.91; H, 7.06. Found: C, 78.76; H, 7.10.

The combined sodium carbonate extracts were acidified with concentrated hydrochloric acid and extracted with ether (3 × 25 mL). The ether solution was washed with water (3 × 25 mL), dried over anhydrous magnesium sulfate, and evaporated to give a mixture of **33** and **35** (70:30, 285 mg, 4.6%, oil). A solution of this oil in ether (4 mL) was treated with excess diazomethane and VPC–chemical ionization mass spectral analysis of the two-component mixture was performed: first component *m/e* 261 (11%), 257 (10%), 230 (16%), 229 (100%), and 145 (6%); second component, identical with authentic methyl ester of **33** (VPC coinjection), 261 (4%), 260 (9%), 257 (10%), 230 (16%), 229 (100%), and 145 (6%). These data indicate that the first component was the methyl ester of 3,3-dimethyl-4-(3-methyl-2-benzo[*b*]furanyl)butanoic acid (**35**).

Rearrangement of Lactone 32. To a stirred solution of lactone **32** (0.49 g, 1.96 mmol) in methylene chloride (3 mL) at −78 °C was added titanium tetrachloride (0.33 mL, 3.0 mmol). After stirring at −78 °C for 2 h, water (1 mL) was added and the solution was extracted with ether (3 × 20 mL). The combined ether extracts were washed with water (3 × 20 mL) and dried over anhydrous magnesium sulfate. Evaporation and crystallization from petroleum ether solvent gave 3,3-dimethyl-4-(2-methyl-3-benzo[*b*]furanyl)butanoic acid (**33**, 0.48 g, 98%, mp 87–88 °C); ^{1}H NMR gave singlets at δ 1.08 (6 H), 2.36 (2 H), 2.37 (3 H), 2.68 (2 H), and a multiplet at 7.11–7.55 (4 H); IR (chloroform) 3.5–3.8 and 5.85 μ.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.01; H, 7.45.

Baeyer–Villiger oxidation of 21 was performed on a 1-g scale by the method described for oxidation of **17a** to give after column chromatography (silica gel, methylene chloride solvent) and crystallization from ether lactone **37** (75%, mp 127–128 °C): ^{1}H NMR δ 1.07 (3 H, singlet), 1.28–1.85 (10 H, multiplet), 2.62 (2 H, multiplet), 5.92 (1 H, singlet), and 6.82–7.35 (4 H, multiplet); IR (chloroform) 5.75, 6.78, and 6.88 μ.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.98; H, 7.49.

Rearrangement of lactone 37 was performed on a 0.4-g scale by the method described for rearrangement of **21** to give tricyclic carboxylic acid **39** (94%, pale yellow oil): ^{1}H NMR δ 1.33 (3 H, singlet), 1.53–2.50 (10 H, multiplet), 2.66 (2 H, multiplet), 7.10–7.48 (4 H, multiplet), and 9.60 (1 H, broad singlet, disappears on addition of deuterium oxide); IR (chloroform) 2.0–3.9, 5.88, and 6.90 μ.

Cyclization of Carboxylic Acid 39. A stirred solution of carboxylic acid **39** (55 mg, 0.2 mmol) in polyphosphoric acid (4 mL) was heated at 110 °C for 0.5 h and then poured into water (20 mL) and extracted with chloroform (3 × 20 mL). The combined extracts were washed with water (3 × 10 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent, thick layer chromatography (silica gel, methylene chloride solvent), and crystallization from petroleum ether gave tetracyclic ketone **40** (18 mg, 33%, mp 101–102 °C): ^{1}H NMR δ 1.33 (3 H, singlet), 1.50–2.22 (8 H, multiplet), 2.80–3.22 (4 H, multiplet), 7.24 (1 H, doublet of doublets, J = 8.0 and 7.6 Hz), 7.52 (1 H, doublet of doublets, J = 8.0 and 1.2 Hz), and 7.94 (1 H, doublet of doublets, J = 7.6 and 1.2 Hz); IR (chloroform) 6.00, 6.19, 6.25, and 7.00 μ; electron impact mass spectrum *m/e* 254 (47%), 239 (100%).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 80:28; H, 7.13. Found: C, 79.89; H, 7.17.

1-Acetoxy-7,7-dimethylbenzocycloheptane-5,9-dione (41). A solution of **34** (84 mg, 0.37 mmol) in methylene chloride (13 mL) at −78 °C was saturated with oxygen for 30 min, then saturated with ozone until a blue coloration developed (5–10 min). The solution was flushed with oxygen for another 30 min at −78 °C after which excess dimethyl sulfide (2 mL) was added. After stirring at room temperature for 2 h, the solvent was evaporated and the residue dissolved in ether (25 mL). The ether solution was washed with water (4 × 15 mL), dried over anhydrous magnesium sulfate, and evaporated to give 1-acetoxy-7,7-dimethylbenzocycloheptane-5,9-dione (**41**, 80 mg, 84%, mp 122.5–123.5 °C): ^{1}H NMR δ 1.20 (6 H, singlet), 2.30 (3 H, singlet), 2.67 (2 H, singlet), 2.70 (2 H, singlet), 7.24 (1 H, doublet of doublets, J = 7.8 and 1.8 Hz), 7.58 (1 H, triplet, J = 7.8 Hz), and 7.76 (1 H, doublet of doublets, J = 7.8 and 1.8 Hz); IR (chloroform) 5.66, 5.91, and 6.25 μ.

1-Acetoxy-7,7-dimethylbenzocycloheptan-9-one (42). A stirred solution of **34** (2.00 g, 8.8 mmol) and *p*-toluenesulfonyl hydrazide (1.79 g, 9.7 mmol) in absolute ethanol was heated to reflux for 24 h. The reaction mixture was cooled in an ice bath and filtered to give the tosylhydrazone of **34** (3.08 g, 89%, mp 168–170 °C dec): ^{1}H NMR δ 1.03 (6 H, singlet), 2.33 (3 H, singlet), 2.40 (3 H, singlet), 2.61 (4 H, broad singlet), 7.06–8.03 (7 H, multiplet).

Following the procedure of Hutchins,[19] a stirred solution of the tosylhydrazone of **34** (2.24 g, 5.65 mmol), sodium cyanoborohydride (1.50 g, 24.0 mmol), bromocresol green indicator, and 5 N hydrochloric acid (pH <4) in dimethylformamide–sulfolane (1:1, 28 mL) was heated to 110 °C for 4 h, and additional acid, sodium cyanoborohydride, and indicator were added as was necessary. After cooling, water (5 mL) was added and the mixture was extracted with ether (3 × 25 mL). The combined ether extracts were washed with water (3 × 25 mL), dried over anhydrous magnesium sulfate, evaporated, column chromatographed (silica gel, petroleum ether solvent), and evaporated to give 2-methyl-3,4-(2,2-dimethylbutano)benzo[*b*]furan (1.03 g, 85%, mp 49.5 °C): ^{1}H NMR δ 1.10 (6 H, singlet), 1.84 (2 H, triplet, J = 6.0 Hz), 2.34 (3 H, singlet), 2.57 (2 H, singlet), 3.07 (2 H, triplet, J = 6.0 Hz), 6.81–7.27 (3 H, multiplet).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.15; H, 8.56.

The ozonolysis procedure was that described for preparation of **41**, and gave, after thick layer chromatography (silica gel, petroleum ether–ether, 9:1) and crystallization from ether–petroleum ether, 1-acetoxy-7,7-dimethylbenzocycloheptan-9-one (**42**, 41%, mp 104–105 °C); ^{1}H NMR δ 1.10 (6 H, singlet), 1.71 (2 H, multiplet), 2.25 (3 H, singlet), 2.60 (2 H, singlet), 2.96 (2 H, broadened triplet, $J \sim 5$ Hz), and 6.86–7.40 (3 H, multiplet); IR (chloroform) 5.72, 5.93, and 6.23 μ.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.36. Found: C, 73.01; H, 7.46.

1-Hydroxy-7,7-dimethylbenzocyclopheptan-5-one (43). To a stirred suspension of lithium aluminum hydride (108 mg, 2.74 mmol) in dry tetrahydrofuran (1 mL) at 0 °C was added a solution of **34** (0.70 g, 3.06 mmol) in dry tetrahydrofuran (4 mL). After refluxing for 20 h, the suspension was cooled to 0 °C and a saturated sodium sulfate solution (0.51 mL, 11.2 mmol) was added slowly. After stirring for 30 min, the mixture was filtered through a pad of anhydrous magnesium sulfate, which was then washed with ether (30 mL). Evaporation of solvent and crystallization from petroleum ether gave pure 2-methyl-3,4-(2,2-dimethyl-4-hydroxybutano)benzo[*b*]furan (0.63 g, 89%, mp 91–92 °C): ^{1}H NMR δ 1.00 (3 H, singlet), 1.12 (3 H, singlet), 1.77 (1 H, singlet, disappears on addition of deuterium oxide), 2.03 (2 H, multiplet), 2.33 (3 H, singlet), 2.53 (2 H, broad singlet), 5.00 (1 H, doublet of doublets, J = 9.0 and 5.4 Hz), and 7.20–7.43 (3 H, multiplet); IR (chloroform) 2.95 and 7.02 μ.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.20; H, 7.87.

The oxonolysis procedure was that described for preparation of **41** (0.45 g, 2.0 mmol), and gave 1-acetoxy-5-hydroxy-7,7-dimethylbenzocycloheptan-9-one (oil): ^{1}H NMR δ 1.00 (6 H, singlet), 1.84

(2 H, doublet, J = 6.0 Hz), 2.20 (3 H, singlet), 2.14 (1 H, broad singlet), 2.63 (2 H, broadened doublet, J = 6.0 Hz), 4.77 (1 H, broadened triplet, J = 5.0 Hz), and 6.90–7.50 (3 H, multiplet).

To a solution of the oil in triethylene glycol (4 mL) was added excess hydrazine (3 mL) and potassium hydroxide (0.71 g, 13 mmol). After heating to reflux for 1 h, the reaction mixture was cooled to 200 °C. Water and excess hydrazine were removed by distillation, after which the reaction mixture was heated at 200 °C for 30 min, cooled to room temperature, and added to water (20 mL). The aqueous solution was washed with ether (3 × 10 mL), acidified with concentrated hydrochloric acid (pH <2), and extracted with ether (3 × 15 mL). The combined ether extracts were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate, and evaporated to give 1-hydroxy-7,7-dimethylbenzocyclopheptan-5-ol (oil).

To a stirred solution of the oil in acetone (5 mL) at 0 °C was added Jones reagent (1.65 mL, 0.82 mmol). After stirring at room temperature for 1.5 h, water (5 mL) was added and the mixture was extracted with ether (3 × 15 mL). The combined ether extracts were washed with water (3 × 15 mL), dried over anhydrous magnesium sulfate, and evaporated. Thick layer chromatography (silica gel, methylene chloride–ether, 9:1) and crystallization from ether–petroleum ether gave 1-hydroxy-7,7-dimethylbenzocycloheptan-5-one (**43**, 0.16 g, 41% from 2-methyl-3,4-(2,2-dimethyl-4-hydroxybutano)benzo[*b*]furan, mp 176–177 °C): ^{1}H NMR δ 1.10 (6 H, singlet), 1.66 (2 H, quintet, J = 2.7 Hz), 2.63 (2 H, singlet), 3.00 (2 H, quintet, J = 2.7 Hz), and 6.83–7.46 (3 H, multiplet); IR (neat) 3.10, 6.01, and 6.85 μ.

Preparation of Hemiacetal 36b. A solution of lactone **32** (16.9 mmol) and sodium methoxide (25.3 mmol) in methanol (85 mL) was stirred in a nitrogen atmosphere at room temperature for 12 h. Aqueous 10% ammonium chloride (200 mL) was added and the resulting mixture was extracted with ether (3 × 100 mL). The combined ether layers were washed with water (2 × 20 mL), dried over anhydrous magnesium sulfate, and evaporated to give **36b** (100%, oil) as a 2:1 mixture of diastereoisomers: selected ^{1}H NMR (hemiacetal methine proton) δ 5.55 (0.33 H, singlet) and 5.90 (0.67 H); IR (neat, mixture) 2.97, 5.80, and 5.87 μ.

Preparation of Thioacetal 44. To a solution of hemiacetal **36b** (501 mg, 1.80 mmol) and ethanedithiol (0.187 g, 1.98 mmol) in ether (0.5 mL), cooled to 0 °C, was added boron trifluoride etherate (0.442 mL, 3.90 mmol). The reaction mixture was stirred at room temperature for 24 h, after which saturated sodium carbonate (20 mL) was added and the resulting mixture was extracted with ether (2 × 30 mL). The combined ether layers were washed with sodium hydroxide (3 × 10 mL) and water (2 × 10 mL), dried over anhydrous magnesium sulfate, evaporated, and crystallized from ether–petroleum ether to give **44** (91%, mp 84–86.5 °C): ^{1}H NMR gave sharp singlets at δ 1.67 (3 H), 1.75 (3 H), 3.12 (4 H), 3.62 (3 H), 6.00 (1 H), a broad singlet at 6.13 (disappears on addition of deuterium oxide), and multiplets at 1.6–2.2 (7 H) and 6.5–7.4 (4 H).

Protection and Desulfurization of the Phenolic Thioacetal 44. To granular sodium hydride (10 mg, 0.42 mmol) was added a solution of phenolic thioacetal **44** (100 mg, 0.28 mmol) in THF (0.3 mL). The mixture was stirred at room temperature for 1 h, after which chloromethyl methyl ether (0.35 mL, 0.61 mmol) was added. After stirring at room temperature for 17 h, water (10 mL) was added and the mixture was extracted with ether (3 × 15 mL). The combined ether layers were washed with water (1 × 10 mL) and saturated sodium chloride, dried over anhydrous magnesium sulfate, and evaporated to give the protected phenolic thioacetal (83 mg, 75%, oil).

Reaction of the oil (0.071 g, 0.178 mmol) with Raney nickel (prepared from 1.5 g of the alloy)[3] in absolute ethanol (1.5 mL) at reflux temperature for 2 h gave, after filtration and solvent evaporation, **45** (0.048 g, 87%, oil): ^{1}H NMR gave singlets at δ 0.87 (6 H), 1.48 (6 H), 2.07 (2 H), 2.10 (2 H), 3.55 (3 H), 3.62 (3 H), 5.23 (2 H), and a multiplet at 7.4–6.7 (4 H).

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