An Unusual Example of a 6-*Endo-Dig* Addition to an Unactivated Carbon–Carbon Triple Bond

Albert Padwa,* Keith E. Krumpe, and M. David Weingarten†

Department of Chemistry, Emory University, Atlanta, Georgia 30322

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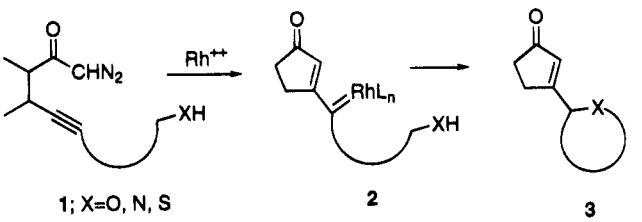
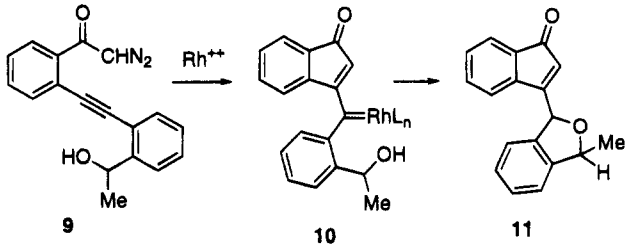
Methyl 2-[2-[2-(1-hydroxy-1-ethyl)phenyl]ethynyl]benzoate was prepared as an intermediate for subsequent conversion to an α-diazo ketone. Under the basic conditions used to hydrolyze the methyl ester, the neighboring hydroxyl functionality underwent reaction with the unactivated acetylenic group, producing a benzopyranyl-substituted α-diazoacetophenone. Treatment of this diazocarbonyl compound with a catalytic quantity of rhodium(II) mandelate afforded a novel dibenzo-[*a*,*e*]cyclononenone derivative. The reaction proceeds *via* an initially formed oxonium ylide which rearranges further by means of a 1,2-alkyl shift. A prime factor in determining the direction of internal cyclization to the triple bond is the presence of the carbomethoxy group in the *ortho* position of the β-phenyl ring. Thus, in contrast with related systems which exhibit a clear preference for 5-*exo-dig* cyclization at the acetylenic center, the 6-*endo-dig* addition is the preferred pathway for the *o*-formyl- and *o*-carbomethoxy-substituted alkynyl alcohols. Careful monitoring of the reaction actually showed that the reaction proceeds by initial formation of the 5-*exo-dig* product followed by a novel rearrangement to the 6-*endo* product.

The rhodium(II)-catalyzed decomposition of diazo compounds continues to find wide application in organic synthesis.[1–4] Cyclopropanation,[5] CH insertion,[6] addition to aromatic rings,[7] and ylide formation[8] are all well-described reactions of rhodium carbenoids. Our own interest in rhodium carbenoid-mediated processes centers on the so-called diazoketo–alkyne metathesis reaction,[9,10] which, despite its potential in synthesis, has been much less widely studied. The process proceeds by addition of the rhodium-stabilized carbenoid onto the acetylenic π-bond.[9] The utility of this reaction would be significantly enhanced if the resulting cyclized vinyl carbenoid intermediate could undergo an intramolecular XH insertion reaction[11] as this would represent a new method for preparing a variety of novel heterocyclic ring systems. In connection with this goal, we synthesized the *o*-acetylenic alcohol **8** as shown in Scheme 1. The synthetic protocol used began with *o*-bromobenzaldehyde and was based on that previously reported for the preparation of related compounds.[9] Thus, methyl 2-[2-[2-(1-hydroxy-1-ethyl)phenyl]ethynyl]benzoate (**8**) was prepared by treating methyl *o*-iodobenzoate with alkynol **7** under typical Castro–Stephens arylation conditions.[12]



Our intention was to convert the ester functionality present in **8** to the corresponding diazoketo group and subject the resulting compound (*i.e.*, **9**) to rhodium(II) catalysis. On the basis of our earlier studies,[9] we assumed that the initially formed rhodium carbenoid would cyclize onto the adjacent acetylenic π-bond and the resulting vinyl carbenoid would undergo a subsequent insertion into the neighboring OH bond to produce indenone **11**.



The carbomethoxyalkynyl-substituted alcohol **8** was subjected to the standard conditions that we had previously used to convert aryl methyl esters to α-diazo

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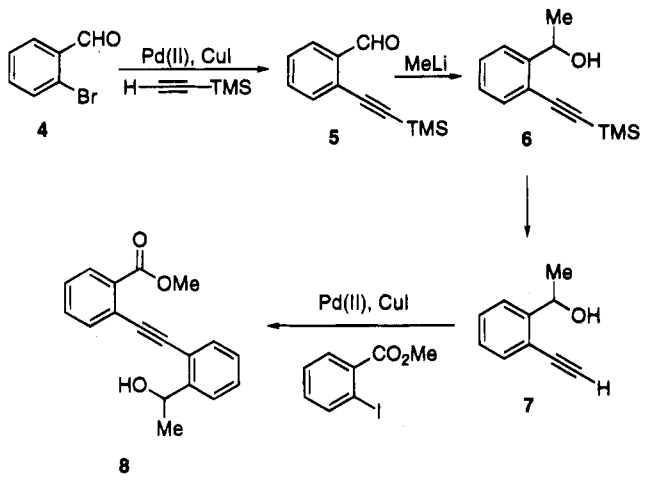
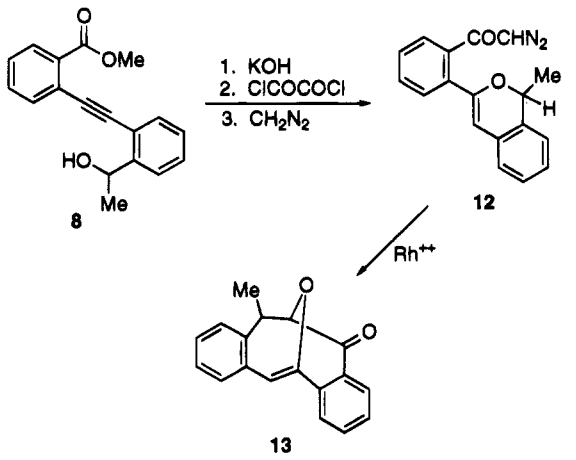
Scheme 1

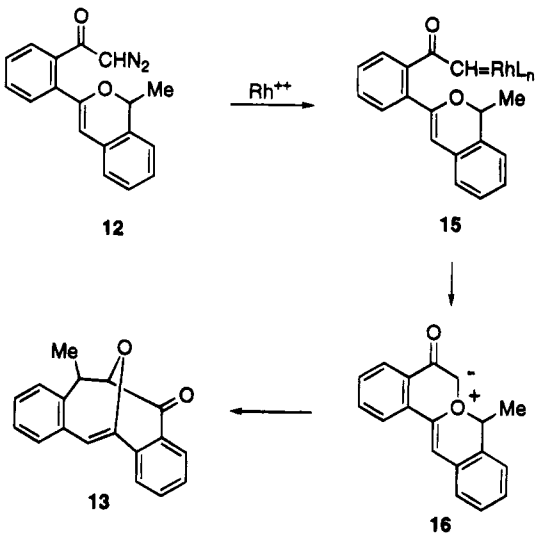


ketones.[9] The resulting α-diazoacetophenone derivative (*i.e.*, **12**) was quite labile and therefore was not isolated but instead was immediately treated with a catalytic quantity of rhodium(II) mandelate. Much to our surprise, the rearranged product isolated in 73% yield corresponded to the novel dibenzo[*a*,*e*]cyclononenone **13**. The



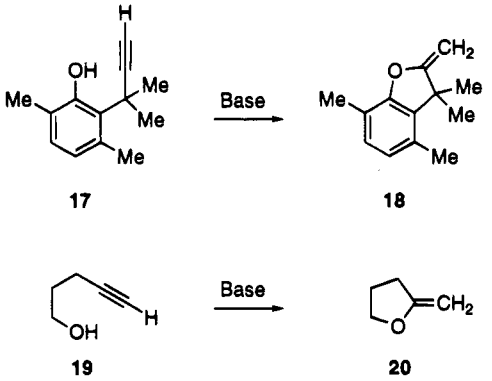
structure of **13** was assigned on the basis of a detailed NMR analysis and firmly established by an X-ray crystallographic study (Figure 1).[13] The compound is not particularly strained even though it formally possesses a bridgehead π-bond. The C−C π-bond distance is 1.317 Å, and the C−C−O bond angle corresponds to 117.2°.

Apparently, under the basic conditions used to hydrolyze the methyl ester, the neighboring hydroxyl functionality had undergone reaction with the nearby acetylenic group, producing the benzopyran ring system. Indeed, when alcohol **8** was treated with base, it smoothly cyclized to the benzopyran ester **14** (*vide infra*). Our view of how **13** is formed from α-diazo ketone **12** is outlined below. Exposure of **12** to the Rh(II) catalyst results in formation of the expected keto carbenoid **15**. It is well-known that metal carbenoids, generated from diazo carbonyl compounds, react with heteroatom-containing substrates to afford ylides.[8] In this case, the initially formed oxonium ylide **16** is transformed into dibenzocyclononenone **13** by means of a 1,2-alkyl shift. Several



groups have previously shown that the rearrangement of oxonium ylides, generated by intramolecular oxygen lone pair insertion of carbenoids, provides a general route to cyclic ethers, thereby providing good precedent for the suggested mechanism.[14-17]

The chance observation that acetylenic alcohol **8** underwent internal cyclization to the triple bond during the base-induced hydrolysis of the methyl ester prompted us to undertake a more detailed study of this process. Results published in the literature with related alkoxide anions (*i.e.*, **17** and **19**) showed that these systems generally prefer to undergo closure to five-membered rings.[18,19] The construction of ring systems by intramo-



lecular addition of an anionic center to a carbon−carbon π-bond has attracted considerable attention in recent years.[20-31] Various organometallic reagents have been

(13) The authors have deposited atomic coordinates for structure **13** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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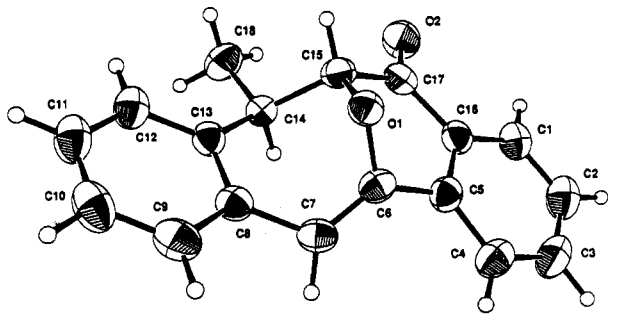
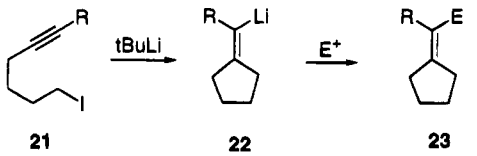


Figure 1. ORTEP representation of dibenzo[*a*,*e*]cyclononenone **13**.

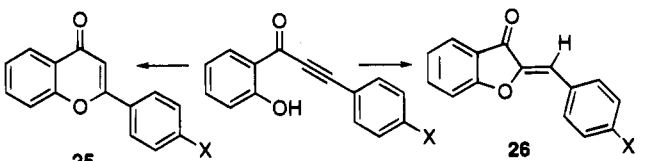
used, resulting in the formation of cyclopentyl-containing products. The synthetic utility of these anionic cyclizations is further enhanced by the ease with which the organometallic product may be functionalized by reaction with various electrophiles. The cyclization of all 5-hexenyl and 5-hexynyl metals studied to date proceeds in a totally regioselective manner to give the corresponding five-membered ring. The isomerization is a thermodynamically favorable process as it produces a C–C β-bond (88 kcal/mol) at the expense of a π-bond (60 kcal/mol). Since questions of angle of approach of an internal nucleophile to the triple bond as well as the degree of involvement of the carbonyl group along the reaction pathway are still of considerable interest, we decided to carry out an exploratory study on the base-induced cyclizations of *o*-ethynylaryl benzylic alcohols of type **8**. As far as we know, this reaction has not yet been investigated in any detail, in spite of the ability of unactivated alkynes to undergo nucleophilic additions with alkoxide ions. Our results are relevant to the understanding of cyclizations involving nucleophilic attack at triple bonds.

The demonstration by Dunitz and Burgi[32] of favored trajectories for the approach of one reactant molecule toward another led to the formulation of rules governing the ease of intramolecular ring closure reactions.[33] Thus, cyclization of the 5-hexenyl anion is predicted to occur by way of a 5-*exo-trig* closure since this pathway permits the optimum trajectory by the nucleophile of 109° to the double bond in the plane of its π-orbitals. For cyclizations involving nucleophilic attack at triple bonds, the situation remains less clear-cut than for the analogous ring closures in tetrahedral or trigonal systems. Thus, the original rules[33] postulated an acute approach angle of about 60° in *dig* systems and stated that the *endo-dig* closures are generally preferred, rather than the *exo-dig* ones, for the formation of five- and six-membered rings. However, subsequent experimental work suggested that, in the case of electronically unbiased acetylenes, *exo-dig* cyclizations are actually favored.[34] For example, Bailey and co-workers have shown that 5-alkyn-1-yllithiums undergo anionic cyclization *via* a highly regiospecific 5-*exo-dig* process involving stereoselective *syn* addition to the triple bond.[35]



21 **22** **23**

It has also been observed that both *exo* and *endo* pathways can occur during the base-induced reaction of 1-(2-hydroxyphenyl)-3-arylprop-2-yn-1-ones (**24**).[36,37] Cyclization of ynone systems of type **24** is reported to give varying amounts of the corresponding flavones **25** and aurones **26**, depending on the substituent groups (X) and the reaction conditions. The observations made with this



25 **24**; X = H, Me, OMe **26**

system strongly suggest that cyclization occurs *via* the respective vinyl carbanions. In this particular case, the inductive effect of the carbonyl group works in favor of flavone production. Moreover, variation of the product distribution as a function of the nature of the β-phenyl ring tends to suggest that there is a competitive balance between the two pathways. The more inductively electron-donating the nature of the β-phenyl ring, the less stable is the aurone carbanion, and hence, less **26** is seen in the product mixture. The possibility of equilibrium formation of the aurone and flavone was discounted by the observation of the same ratio of products over varying times of reaction. In addition, both the flavone and aurone rings have been observed not to ring open under various basic conditions.[38] Thus, the cyclization of the *o*-hydroxyaryl phenylethynyl ketone **24** in basic media lies close to the dividing line between the 6-*endo-dig* and 5-*exo-dig* modes, since the direction of the ring closure is strongly influenced by changes in the experimental conditions. There have also been several theoretical studies which indicate that the favored path of approach of a nucleophile to a triple bond is at an obtuse angle of 120–127°.[39-43]

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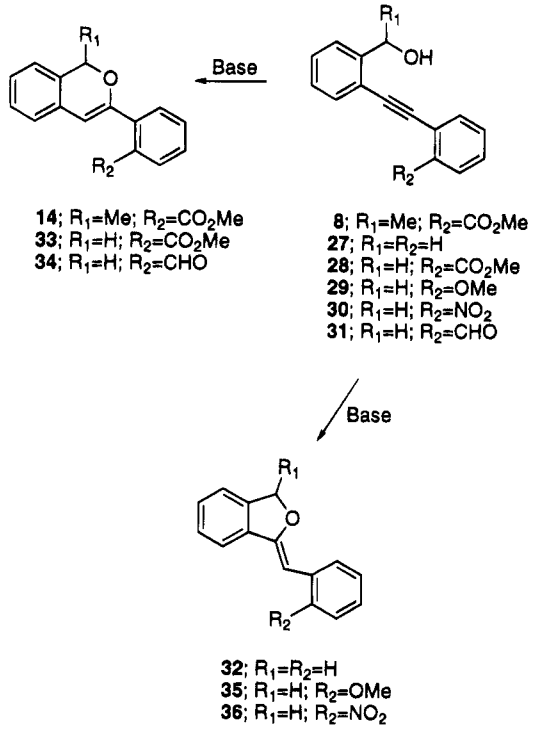
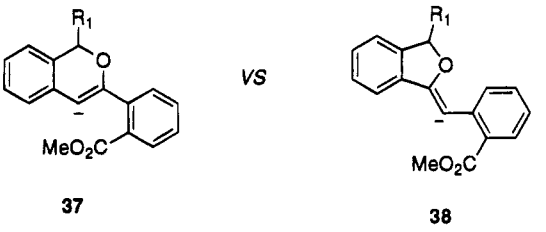
One of the first things we discovered while examining the base-induced reaction of the *o*-ethynylaryl-substituted benzylic alcohol system is that the mode of cyclization is markedly dependent upon the presence of the carbomethoxy group in the *ortho* position of the β-phenyl ring.[44] Thus, treating a sample of 2-(hydroxymethyl)-1-(2-phenylethynyl)benzene (**27**) in KOH/MeOH resulted in exclusive 5-*exo-dig* ring closure which led to the isolation of 1-(phenylmethylidene)-1,3-dihydroisobenzofuran (**32**) in 95% yield. This was to be expected in view of related reports in the literature.[18,19,36–38,45,46] However, an entirely different result was obtained when the cyclizations of the *o*-carbomethoxyaryl alkynols (**8** and **28**) were carried out under similar experimental conditions. With these systems, only the products of 6-*endo-dig* closure (**14** and **33**) were obtained.

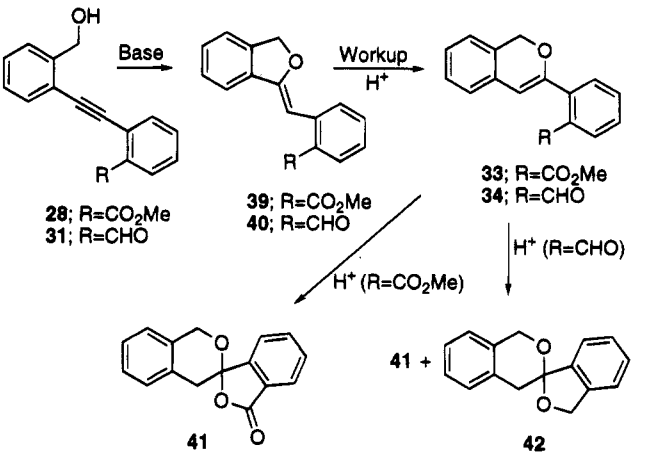
Since it appeared that the 6-*endo* cyclization of these alcohols was dependent upon the presence of an electron-withdrawing group in the *ortho* position, we prepared the corresponding alkynyl alcohols **29** (R_2 = OMe), **30** (R_2 = NO_2), and **31** (R_2 = CHO). The 6-*endo-dig* cyclization product **34** was exclusively formed with **31**, but only the 5-*exo-dig* process occurred with **29** and **30**. The inductive effect of the carbonyl group should have worked in favor of dihydroisobenzofuran production, but this is clearly not the case. It should also be noted that the carbomethoxy group is not involved in conjugate interaction with the reacting alkoxide center at any point along the reaction coordinate. Treatment of these alkynyl-substituted alcohols with NaH/THF (aprotic) instead of KOH/MeOH (protic) did not change the product distribution. This result would tend to rule out the possibility of carbanion interconversion (*i.e.*, **38** → **37**).[38]





37 **38**

The fact that 6-*endo* cyclization mode only occurs when a carbonyl group is present in the *ortho* position of the aromatic ring prompted us to study the reaction in greater detail. The product distribution was found to be markedly dependent upon the reaction conditions. Careful monitoring of the crude mixture by NMR spectroscopy showed that the reaction proceeded by initial formation of the 5-*exo-dig* products (*i.e.*, **39** and **40**) followed by subsequent rearrangement to the 6-*endo* product. Thus, these apparent 6-*endo* cyclizations are actually the consequence of a 5-*exo* cyclization followed by an acid-catalyzed rearrangment. Although we were unable to isolate benzofurans **39** and **40** due to their facile conversion to benzopyrans **33** and **34**, their structures were confirmed by ozonolysis of the crude reaction mixture to phthalide and the corresponding aryl aldehydes. It should also be noted that further treatment of benzopyran **33** with acid resulted in the formation of lactone **41**. In a related manner, the reaction of **34** with mild acid afforded a 1:1 mixture of lactone **41** and lactol **42**.



A plausible mechanism for the acid-catalyzed rearrangment of **39** to **33** is outlined in Scheme 2. The first step involves initial protonation of benzofuran **39** followed by an intramolecular cyclization of the *ortho* carbonyl group to form spiroketal **43** which then proceeds to benzopyran **33** *via* a series of reactions. Ring expansion by a 1,2-oxygen shift results in the formation of cation **44** which undergoes proton loss to produce **45**. This is followed by a 1,5-sigmatropic hydrogen shift and a subsequent cycloreversion to give the final product. Further reaction of **33** with acid results in the formation of spirolactone **41**. Benzofuran **40** undergoes a related sequence, ultimately affording lactol **51** which proceeds

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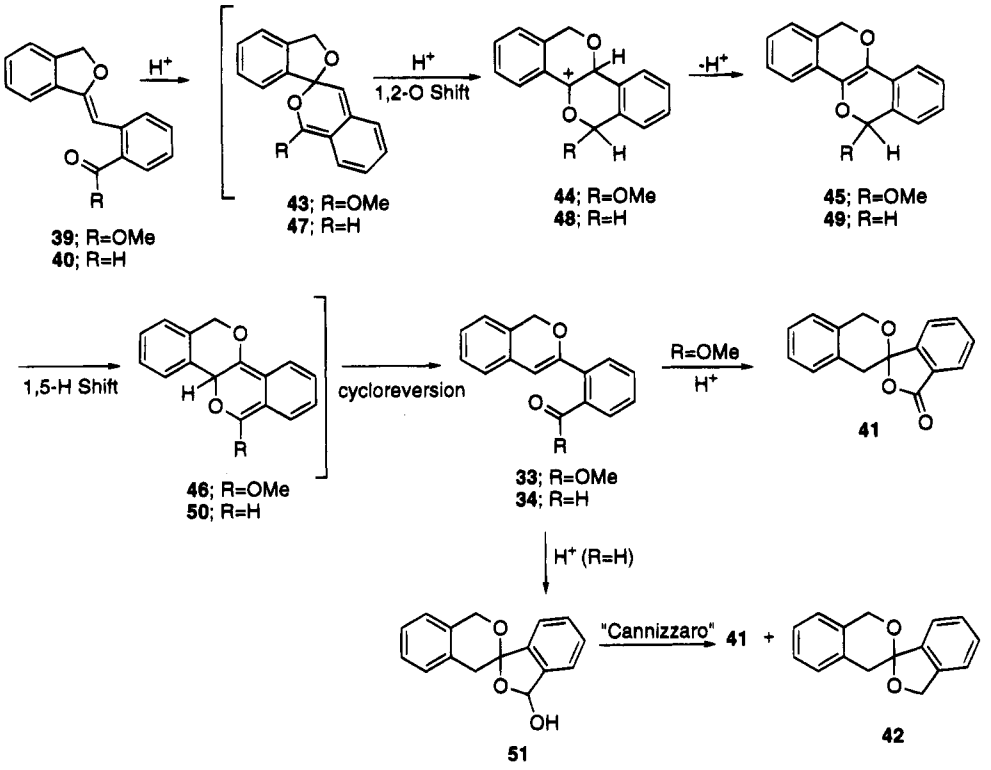
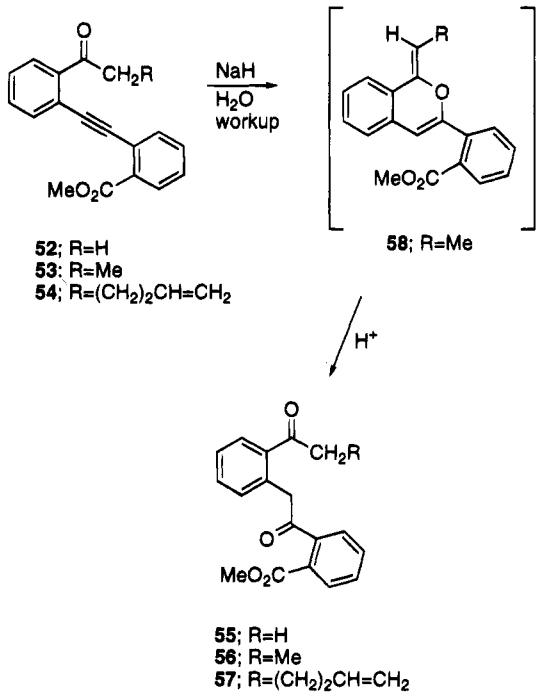
Scheme 2



to lactone **41** and spiroketal **42** *via* an acid-catalyzed Cannizzaro reaction.[47]

In an extension of this work, we also examined the base-induced reaction of several keto aryl alkynyl esters so as to evaluate the mode of internal cyclization. Nucleophilic addition of carbon enolates to triple bonds is a well-known process.[48] The question of interest here was whether the cyclization would occur in a 5-*exo*- or 6-*endo-dig* fashion. We found that the base-induced cyclization (NaH/THF) of **52** afforded a single product in 83% yield whose structure was identified as methyl 2-[2-[2-(1-oxoethyl)phenyl]-1-oxoethyl]benzoate (**55**). Similar transformations occurred with ketones **53** (R = Me) and **54** (R = $(CH_2)_2CH{=}CH_2$). In the case of **53**, workup of the reaction mixture was carried out in a fashion so as to minimize acid contact. Under these conditions, benzopyran **58** was isolated in 60% yield. Further treatment of **58** with aqueous acid afforded ketone **56** in high yield. We assume that related benzopyrans are also formed in the base-induced reactions of ketones **52** and **54**. With the above systems, attack of the enolate oxygen atom on the acetylenic π-bond could occur in a 6-*endo-dig* manner, leading to the six-membered benzopyran ring which is subsequently hydrolyzed under the acidic conditions. Alternatively, the cyclization could proceed in a 5-*exo-dig* manner and the initially formed product could rearrange to the observed diketone under workup conditions.

In conclusion, we have studied the base-induced cyclization reaction of several (phenylethynyl)aryl-substituted alcohols and ketones where the neighboring oxygen atom was found to readily add to the unactivated triple bond. The apparent 6-*endo-dig* addition is actually the consequence of a novel acid-catalyzed rearrangement of



the initially formed benzofuran derivative. Further studies on the mechanistic details and synthetic potential of these cyclization are in progress.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of extra dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless specified otherwise.

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Rhodium(II)-Catalyzed Reaction of 2-(1-Methyl-1*H*-2-benzopyran-3-yl)-α-diazoacetophenone (12). To a deaerated solution of 18.5 g (0.1 mol) of 2-bromobenzaldehyde, 15.0 g (0.15 mol) of (trimethylsilyl)acetylene, and 400 mg (1.52 mmol) of triphenylphosphine in 300 mL of anhydrous triethylamine were added 200 mg (0.89 mmol) of palladium(II) acetate and 30 mg of CuI under Ar. The mixture was heated to 80 °C for 5 h. After cooling, the mixture was filtered and concentrated. The dark brown residue was mixed with 100 mL of water and extracted with CH_2Cl_2. The combined organic phase was dried, concentrated, and distilled under reduced pressure (93–94 °C (0.5 mm)) to give 16.4 g (81%) of 2-[2-(trimethylsilyl)ethynyl]benzaldehyde: mp 59–60 °C (lit.[49] mp 60–61 °C); IR (neat) 2170, 1695, 1255, 865, and 770 cm^{-1}; ^1H-NMR ($CDCl_3$, 90 MHz) δ 0.30 (s, 9H), 7.30–7.60 (m, 3H), 7.80–8.00 (m, 1H), and 10.6 (s, 1H).

To a solution containing 4.0 g (19.7 mmol) of the above aldehyde in 200 mL of anhydrous THF was added dropwise at 0 °C 15.5 mL of a 1.0 M methyllithium solution. After stirring for 2 h at rt under N_2, the reaction mixture was poured over ice and acidified to neutral pH with a 10% aqueous HCl solution. The aqueous solution was extracted with ether. The ether extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Chromatography of the residue on silica gel gave 3.21 g (74%) of 2-(1-hydroxyethyl)-1-[2-(trimethylsilyl)ethynyl]benzene: IR (neat) 2160, 1250, 1075, 860, and 765 cm^{-1}; ^1H-NMR ($CDCl_3$, 90 MHz) δ 0.30 (s, 9H), 1.50 (d, 3H, J = 6.0 Hz), 2.40 (m, 1H), 5.15–5.50 (m, 1H), and 7.05–7.60 (m, 4H).

To a solution containing 3.21 g (14.5 mmol) of the above alcohol and 5.0 mL of water in 150 mL of THF was added 44.1 mL of a 1.0 M tetrabutylammonium fluoride solution at 0 °C. The mixture was stirred for 16 h at 25 °C, and then the reaction was diluted with ether and washed successively with a saturated aqueous ammonium chloride solution, water, and brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 1.5 g (70%) of 2-(1-hydroxyethyl)-1-ethynylbenzene: IR (neat) 2110, 1445, 1070, and 790 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, 3H, J = 6.3 Hz), 2.88 (brs, 1H), 3.30 (s, 1H), 5.53 (q, 1H, J = 6.3 Hz), 7.18 (t, 1H, J = 7.4 Hz), 7.34 (t, 1H, J = 7.7 Hz), 7.44 (d, 1H, J = 7.4 Hz), and 7.51 (d, 1H, J = 7.7 Hz).

To a deaerated solution containing 1.36 g (9.3 mmol) of the above acetylene and 2.36 g (9.0 mmol) of methyl 2-iodobenzoate in 100 mL of distilled triethylamine were added 30 mg of *bis*(triphenylphosphine)palladium(II) chloride and 60 mg of CuI under Ar. The mixture was heated at 60 °C for 16 h, cooled, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was chromatographed on silica gel to give 2.13 g (82%) of methyl 2-[2-[2-(1-hydroxy-1-ethyl)phenyl]ethynyl]benzoate (**8**): IR (neat) 2220, 1730, 1265, 1075, and 760 cm^{-1}; ^1H-NMR ($CDCl_3$, 90 MHz) δ 1.55 (d, 3H, J = 6.0 Hz), 3.40 (d, 1H, J = 5.0 Hz), 3.93 (s, 3H), 5.35 (m, 1H), 7.20–7.80 (m, 7H), and 7.90–8.05 (m, 1H). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.11; H, 5.76. Found: C, 77.19; H, 5.83.

A solution containing 1.0 g (3.57 mmol) of the above hydroxy ester, 0.60 g of KOH, 2 mL of water, and 50 mL of methanol was heated at 70 °C for 5 h. After the solution was cooled, the methanol was removed under reduced pressure and the aqueous residue was diluted with 20 mL of water. The solution was acidified with 3.8 mL of a 10% solution of HCl and extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to a volume of 25 mL. To this solution were added 1.8 mL of oxalyl chloride and a catalytic amount of dimethylformamide. After stirring for 2 h, the solution was concentrated under reduced pressure, and the brown residue was redissolved in 20 mL of CH_2Cl_2. The reaction mixture was treated with an ethereal diazomethane solution (33 mmol) at 25 °C and stirred for 16 h. After concentration under reduced pressure, the resulting residue was chromatographed on silica gel to give 570 mg (41%) of 2-(1-methyl-1*H*-2-benzopyran-3-yl)-α-diazoacetophenone (**12**): IR (neat) 2110, 1760, 1615, 1350, and 770 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.56 (d, 3H, J = 6.4 Hz), 5.55 (q, 1H, J = 6.4 Hz), 5.83 (brs, 1H), 6.23 (s, 1H), and 7.00–7.80 (m, 8H).

To a solution containing 3 mg of rhodium(II) mandelate in 5 mL of anhydrous CH_2Cl_2 was added dropwise a solution of 148 mg (0.51 mmol) of **12** in 10 mL of CH_2Cl_2 under N_2. The reaction mixture was stirred for an additional 16 h at rt. The mixture was filtered though a pad of Celite and concentrated under reduced pressure. Recrystallization of the solid residue from an ether/hexane mixture afforded 103 mg of a pale yellow solid (73%) which was identified as 11,12-dihydro-6,12-epoxy-13-methyl-13*H*-dibenzo[*a*,*e*]cyclononen-11-one (**13**) on the basis of its spectral properties: mp 159–160 °C; IR (neat) 1675, 1600, 1080, 1045, and 840 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.53 (d, 3H, J = 6.8 Hz), 3.23 (dq, 1H, J = 11.0 and 6.8 Hz), 4.65 (d, 1H, J = 11.0 Hz), 6.71 (s, 1H), 7.30–7.70 (m, 7H), and 8.10 (d, 1H, J = 7.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.2, 36.7, 96.7, 119.7, 121.0, 125.6, 126.3, 127.0, 127.1, 127.7, 128.1, 132.4, 133.5, 136.6, 138.8, 141.3, 152.4, and 193.9. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.37. Found: C, 82.17; H, 5.42. The X-ray structure of **13** was solved by direct methods using the SHELXTL program.[13]

Reaction of Methyl 2-[2-[2-(1-Hydroxy-1-ethyl)phenyl]-ethynyl]benzoate (8) with Sodium Hydride. To a solution of 116 mg of NaH (60%) in 20 mL of anhydrous THF was added a solution of 406 mg (1.45 mmol) of **8** in 20 mL of anhydrous THF under N_2. After heating at reflux for 4 h, the reaction mixture was poured over ice, acidified with a 10% solution of aqueous HCl, and extracted with ether. The combined ether extracts were washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. Chromatography of the residue on silica gel afforded 180 mg (90%) of methyl 2-(1-methyl-1*H*-2-benzopyran-3-yl)benzoate (**14**): IR (CH_2Cl_2) 1713, 1645, 1254, 1040, and 756 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 1.60 (d, 3H, J = 6.5 Hz), 3.91 (s, 3H), 5.72 (q, 1H, J = 6.5 Hz), 7.08 (s, 1H), 7.15–7.40 (m, 4H), 7.50 (t, 1H, J = 7.6 Hz), 7.66 (d, 1H, J = 7.2 Hz), 7.92 (d, 1H, J = 7.8 Hz), and 8.46 (d, 1H, J = 8.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.5, 51.8, 82.5, 92.6, 120.4, 124.5, 126.9, 128.1, 129.0, 129.4, 130.5, 131.6, 134.6, 137.3, 143.8, 156.7, and 168.3. Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.11; H, 5.76. Found: C, 77.02; H, 5.62.

Reaction of 2-(Hydroxymethyl)-1-(2-phenylethynyl)-benzene (27) with Potassium Hydroxide. To a deaerated solution containing 5.85 g (25.0 mmol) of 2-iodobenzyl alcohol and 2.86 g (25.0 mmol) of phenylacetylene in 200 mL of triethylamine were added 30 mg of bis(triphenylphosphine)-palladium(II) chloride and 30 mg of CuI under Ar. The reaction mixture was heated at reflux for 12 h. After cooling, the mixture was filtered and concentrated under reduced pressure. Chromatography of the resulting brown oil on silica gel gave 5.0 g (96%) of 2-(hydroxymethyl)-1-(2-phenylethynyl)-benzene (**27**): mp 65–66 °C; IR (CH_2Cl_2) 1605, 1500, 1040, and 1010 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 3.00 (brs, 1H), 4.91 (s, 2H), 7.20–7.43 (m, 5H), and 7.46–7.62 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 63.0, 86.3, 93.7, 120.5, 122.4, 126.4, 126.7, 127.9, 128.2, 131.0, 131.5, and 142.0.

To a solution of 160 mg of KOH in 5 mL of water and 20 mL of methanol was added 200 mg (0.96 mmol) of **27**. The mixture was heated at reflux for 6 h, after which time the methanol was removed under reduced pressure. The resulting residue was diluted with 15 mL of water and acidified with a solution of 10% aqueous HCl. After the aqueous solution was extracted with ether, the organic phase was separated and dried over magnesium sulfate. Removal of the solvent under reduced pressure afforded 0.19 g (95%) of 1-(phenylmethylidene)-1,3-dihydroisobenzofuran (**32**): IR (CH_2Cl_2) 1656, 1466, 1372, and 1038 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz) δ 5.53 (s, 2H), 6.06 (s, 1H), 7.25–7.53 (m, 6H), 7.60–7.65 (m, 1H), and 7.90 (d, 1H, J = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 74.9, 96.2, 119.9, 121.2, 125.3, 127.8, 128.0, 128.4, 128.7, 134.8, 136.4, 139.2, and 156.4. Anal. Calcd for $C_{15}H_{12}O$: C, 86.50; H, 5.81. Found: C, 86.34; H, 5.58.

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Reaction of Methyl 2-[2-[2-(Hydroxymethyl)phenyl]-ethynyl]benzoate (28) with Sodium Hydride. To a deaerated solution containing 0.82 g (3.5 mmol) of 2-iodobenzyl alcohol and 0.60 g (4.16 mmol) of methyl 2-ethynylbenzoate in 50 mL of triethylamine were added 20 mg of bis(triphenylphosphine)palladium(II) chloride and 20 mg of CuI under an argon atmosphere. The reaction mixture was heated at reflux for 12 h. After cooling, the mixture was filtered and concentrated under reduced pressure. Chromatography of the resulting brown oil on silica gel gave 0.75 g (80%) of methyl 2-[2-[2-(hydroxymethyl)phenyl]ethynyl]benzoate (**28**): IR (CH_2Cl_2) 1717, 1294, 1255, 1076, and 756 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.90 (s, 3H), 4.11 (t, 1H, J = 6.3 Hz), 4.82 (d, 2H, J = 6.3 Hz), 7.23–7.40 (m, 4H), 7.49 (t, 1H, J = 7.5 Hz), 7.56 (d, 1H, J = 7.0 Hz), 7.64 (d, 1H, J = 7.6 Hz), and 7.98 (d, 1H, J = 7.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 52.4, 63.9, 92.3, 92.5, 121.8, 123.8, 127.3, 127.9, 128.1, 128.8, 130.4, 130.6, 131.9, 132.5, 134.2, 143.5, and 166.4.

To a solution of 40 mg of NaH (60%) in 10 mL of anhydrous THF was added a solution of 200 mg (0.75 mmol) of **28** in 10 mL of anhydrous THF under N_2. After stirring for 6 h at rt, the reaction mixture was concentrated on the rotary evaporator to give 1-[2-(carbomethoxy)benzylidene]-1,3-dihydroisobenzofuran (**39**) as an extremely labile compound whose ^{1}H-NMR contains singlets at 3.84 (3H), 5.33 (2H), and 6.58 (1H). The structural assignment of **39** was verified by ozonolysis to give phthalide and methyl 2-formylbenzoate[50] which matched authentic samples in all regards.

Benzofuran **39** was treated with a solution of saturated ammonium chloride and immediately extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water and brine and then dried over magnesium sulfate. Evaporation of the solvent under reduced pressure afforded 120 mg (60%) of methyl 2-(1*H*-2-benzopyran-3-yl)benzoate (**33**): mp 72–73 °C; IR (CH_2Cl_2) 1716, 1648, 1485, 1258, and 1037 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.92 (s, 3H), 5.47 (s, 2H), 7.06 (s, 1H), 7.16 (t, 1H, J = 7.6 Hz), 7.25–7.40 (m, 3H), 7.48 (t, 1H, J = 7.4 Hz), 7.67 (m, 1H), 7.91 (d, 1H, J = 8.0 Hz), and 8.39 (d, 1H, J = 8.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 51.8, 74.9, 92.9, 120.5, 121.0, 124.6, 127.0, 128.0, 129.0, 129.3, 130.5, 131.6, 134.8, 137.1, 139.2, 157.5, and 168.3. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.66; H, 5.30. Found: C, 76.53; H, 5.22.

Benzopyran **33** was further treated with a saturated ammonium chloride solution and stirred at rt for 10 min. The combined CH_2Cl_2 extracts were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. Chromatography of the residue on silica gel afforded 3′-oxospiro[3*H*-1,4-dihydro-2-benzopyran-3,1′(3′*H*)-isobenzofuran] (**41**): mp 209–210 °C; IR (neat) 2030, 2868, 1700, and 1603 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.58 (AB, 2H, J = 16.2 Hz), 5.16 (AB, 2H, J = 12.9 Hz), 7.30–7.65 (m, 7H), and 8.16 (d, 1H, J = 7.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 36.9, 72.7, 112.8, 121.4, 122.1, 124.9, 127.8, 128.0, 128.1, 130.1, 130.2, 134.0, 136.5, 137.7, 139.9, and 164.2. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.08; H, 4.84.

Reaction of [2-[2-(2-Methoxyphenyl)ethynyl]phenyl]-methanol (29) with Sodium Hydride. To a deaerated solution containing 2.8 mL (21.5 mmol) of 2-iodoanisole and 4.0 mL (28.3 mmol) of (trimethylsilyl)acetylene in 300 mL of triethylamine were added 200 mg of bis(triphenylphosphine)-palladium(II) chloride, 25 mg of triphenylphosphine, and 300 mg of CuI under a nitrogen atmosphere. The reaction mixture was heated at reflux for 8 h. After cooling, the mixture was filtered and concentrated under reduced pressure. The residue was diluted with ether and washed with a saturated aqueous ammonium chloride solution. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. To a solution containing the crude acetylene in 100 mL of THF was added 40 mL of a 1.0 M tetrabutylammonium fluoride solution at 0 °C. The mixture was stirred for 1 h at 25 °C, and then the reaction mixture was diluted with ether and washed successively with a saturated aqueous ammonium chloride solution, water, and brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 2.24 g (79.2%) of 1-ethynyl-2-methoxybenzene:[51] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.29 (s, 1H), 3.87 (s, 3H), and 6.84–7.46 (m, 4H).

To a deaerated solution containing 1.88 g (14.2 mmol) of the above acetylene and 3.35 g (14.3 mmol) of 2-iodobenzyl alcohol in 100 mL of triethylamine were added 50 mg of bis-(triphenylphosphine)palladium(II) chloride, 10 mg of triphenylphosphine, and 100 mg of CuI under a nitrogen atmosphere. The reaction mixture was heated at reflux for 8 h. After cooling, the mixture was filtered and concentrated under reduced pressure. Chromatography of the resulting brown oil on silica gel gave 2.0 g (60%) of [2-[2-(2-methoxyphenyl)-ethynyl]phenyl]methanol (**29**): IR (neat) 3402, 3061, 2207, and 1588 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 1H), 3.90 (s, 3H), 4.83 (s, 2H), and 6.87–7.55 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.8, 64.6, 90.7, 91.8, 110.5, 112.1, 120.7, 122.1, 127.5, 128.0, 128.5, 130.1, 131.8, 132.6, 143.3, and 160.1.

To a solution of 40 mg of NaH (60%) in 20 mL of anhydrous THF was added a solution of 200 mg (0.84 mmol) of **29** under N_2. After stirring for 6 h at rt, the reaction mixture was acidified with a saturated ammonium chloride solution, extracted with CH_2Cl_2, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure afforded 200 mg (100%) of 1-(2-methoxybenzylidene)-1,3-dihydroisobenzofuran (**35**): mp 138–139 °C; IR (neat) 3069, 2930, 1651, and 1243 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.50 (s, 2H), 6.41 (s, 1H), 6.87 (d, 1H, J = 8.1 Hz), 6.96–7.66 (m, 6H), and 8.25 (dd, 1H, J = 7.8 and 1.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.6, 74.7, 89.4, 110.3, 120.2, 120.7, 121.1, 125.3, 126.3, 128, 128.5, 128.7, 135.2, 139.1, 155.6, and 156.3. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.49; H, 6.00.

Reaction of [2-[2-(2-Nitrophenyl)ethynyl]phenyl]methanol (30) with Sodium Hydride. To a deaerated solution containing 5.0 g (20.1 mmol) of 1-iodo-2-nitrobenzene and 3.6 mL (25.5 mmol) of (trimethylsilyl)acetylene in 300 mL of triethylamine were added 200 mg of bis(triphenylphosphine)-palladium(II) chloride, 25 mg of triphenylphosphine, and 300 mg of CuI under a nitrogen atmosphere. After stirring for 6 h at rt, the mixture was filtered and concentrated under reduced pressure. The residue was diluted with ether and washed successively with a saturated aqueous ammonium chloride solution. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. To a solution containing the crude acetylene in 100 mL of THF was added 40 mL of a 1.0 M tetrabutylammonium fluoride solution at 0 °C. The mixture was stirred for 1 h at 25 °C, and then the reaction mixture was diluted with ether and washed successively with a saturated aqueous ammonium chloride solution, water, and brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 1.8 g (60.3%) of 1-ethynyl-2-nitrobenzene:[52] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.49 (s, 1H), 7.45–7.60 (m, 2H), 7.67 (d, 1H, J = 8.1 Hz), and 8.02 (d, 1H, J = 8.1 Hz).

To a deaerated solution containing 1.68 g (11.5 mmol) of the above acetylene and 2.75 g (11.75 mmol) of 2-iodobenzyl alcohol in 100 mL of triethylamine were added 50 mg of bis-(triphenylphosphine)palladium(II) chloride, 10 mg of triphenylphosphine, and 100 mg of CuI under a nitrogen atmosphere. The reaction mixture was heated at reflux for 8 h. After cooling, the mixture was filtered and concentrated under reduced pressure. Chromatography of the resulting brown oil on silica gel gave 1.8 g (62%) of [2-[2-(2-nitrophenylethynyl)]-phenyl]methanol (**30**): IR (neat) 3253, 2911, 2214, and 1517 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 1H), 4.92 (s, 2H), 7.23–7.62 (m, 6H), 7.71 (d, 1H, J = 8.1 Hz) and 8.08 (d, 1H, J = 8.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 63.8, 89.2, 94.9, 118.6, 120.6, 124.6, 127.5, 127.7, 128.8, 129.7, 132.8, 133.1, 134.8, 143.5, and 149.4.

(50) Baum, J. S.; Staveski, M. M. *Synth. Commun.* **1989**, *19*, 2283.

(51) Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3539.

(52) Takahashi, S.; Kuroyama, Y.; Hagihara, N. *Synthesis* **1980**, 627.

To a solution of 40 mg of NaH (60%) in 20 mL of anhydrous THF was added a solution of 200 mg (0.79 mmol) of **30** under N_2. After stirring for 6 h at rt, the reaction mixture was acidified with a saturated ammonium chloride solution, extracted with CH_2Cl_2, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure afforded 200 mg (100%) of 1-(2-nitrobenzylidene)-1,3-dihydro-isobenzofuran (**36**): mp 139–141 °C; IR (neat) 1644, 1589, 1513, and 752 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.52 (s, 2H), 6.52 (s, 1H), 7.16–7.65 (m, 6H), 7.85 (d, 1H, J = 8.4 Hz) and 8.39 (d, 1H, J = 8.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 75.4, 89.2, 120.9, 121.2, 124.6, 125.2, 128.4, 129.8, 130.1, 130.9, 132.3, 134.2, 139.6, 147.1, and 159.7. Anal. Calcd for $C_{15}H_{11}N_1O_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.85; H, 4.43; N, 5.47.

Reaction of 2-[2-[2-(Hydroxymethyl)phenyl]ethynyl]-benzaldehyde (31) with Sodium Hydride. To a deaerated solution containing 5.0 g (21.4 mmol) of 2-iodobenzyl alcohol and 4.5 mL (31.8 mmol) of (trimethylsilyl)acetylene in 200 mL of triethylamine were added 200 mg of bis(triphenylphosphine)palladium(II) chloride, 20 mg of triphenylphosphine, and 100 mg of CuI under a nitrogen atmosphere. The reaction mixture was heated at reflux for 48 h. After cooling, the mixture was filtered and concentrated under reduced pressure. The residue was diluted with ether and washed successively with a saturated aqueous ammonium chloride solution. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. To a solution containing the crude alcohol in 100 mL of THF was added 25 mL of a 1.0 M tetrabutylammonium fluoride solution at 0 °C. The mixture was stirred for 1 h at rt, and then the reaction mixture was diluted with ether and washed successively with water and brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 2.6 g (91%) of (2-ethynylphenyl)methanol: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.10 (bs, 1H), 3.32 (s, 1H), 4.82 (s, 2H), and 7.22–7.50 (m, 4H).

To a deaerated solution containing 0.57 g (4.3 mmol) of the above alcohol and 1.0 g (4.3 mmol) of 2-iodobenzaldehyde in 20 mL of triethylamine were added 75 mg of bis(triphenylphosphine)palladium(II) chloride, 20 mg of triphenylphosphine, and 50 mg of CuI under a nitrogen atmosphere. After stirring at rt for 8 h, the mixture was filtered and concentrated under reduced pressure. Chromatography of the resulting brown oil on silica gel gave 0.92 g (91%) of 2-[2-[2-(hydroxymethyl)phenyl]ethynyl]benzaldehyde (**31**): IR (neat) 3246, 2826, 2741, 2207, and 1695 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.72 (s, 1H), 4.89 (s, 2H), 7.23–7.65 (m, 7H), 7.90 (d, 1H, J = 7.8 Hz) and 10.49 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 63.8, 89.9, 93.6, 120.7, 125.6, 127.5, 127.6, 128.7, 128.9, 129.4, 132.5, 133.6, 133.8, 135.7, 142.9, and 191.6.

To a solution of 51 mg of NaH (60%) in 15 mL of anhydrous THF was added 300 mg (1.3 mmol) of **31** under N_2. After stirring for 6 h at rt, the reaction mixture was concentrated under reduced pressure to give 1-(2-formylbenzylidene)-1,3-dihydroisobenzofuran (**40**) as a very labile compound whose ^{1}H-NMR shows singlets at 6.42 (1H) and 10.38 (1H). The structural assignment of **40** was verified by ozonolysis to give phthalide and *o*-phthalaldehyde which matched authentic samples in all regards.

Benzofuran **40** was acidified with a saturated ammonium chloride solution and immediately extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were concentrated under reduced pressure to give 2-(1*H*-2-benzopyran-3-yl)benzaldehyde (**34**) which showed singlets at 5.50 (2H), 7.12 (1H), and 10.24 (1H) in the ^{1}H-NMR. Benzopyran **34** was further treated with an ammonium chloride solution and extracted with CH_2Cl_2, and the solvent was removed under reduced pressure. Chromatography on silica gel afforded 106 mg (68%) of 3′-oxospiro-[3*H*-1,4-dihydro-2-benzopyran-3,1′(3′*H*)-isobenzofuran] (**41**) and 100 mg (66%) of spiro[3*H*-1,4-dihydro-2-benzopyran-3,1′(3′*H*)-isobenzofuran] (**42**): IR (neat) 3025, 2933, 2897, and 2855 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.34 (AB, 2H, J = 16.3 Hz), 5.02 (AB, 2H, J = 14.8 Hz), 5.17 (AB, 2H, J = 12.7 Hz), and 7.00–7.50 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 36.9, 64.4, 71.6, 107.5, 121.3, 122.0, 124.0, 126.3, 126.8, 127.8, 128.9, 129.2, 131.5, 133.87, 140.1, and 140.6; HRMS calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0994.

Reaction of Methyl 2-[2-[2-(1-Oxoethyl)phenyl]ethynyl]benzoate (52) with Sodium Hydride. To a solution of 1.3 g (6.0 mmol) of pyridinium chlor chromate in 10 mL of anhydrous CH_2Cl_2 was added a solution of 1.0 g (3.57 mmol) of 2-[2-[2-(1-hydroxy-1-ethyl)phenyl]ethynyl]benzoate (**8**) in 20 mL of CH_2Cl_2 at rt under N_2. After stirring for 4 h, the mixture was poured into 50 mL of ether, and the remaining residue was washed with ether. The combined ether solutions were filtered though a short column of Florisil and evaporated under reduced pressure. Chromatography of the residue on silica gel afforded 550 mg (94%) of methyl 2-[2-[2-(1-oxoethyl)phenyl]-ethynyl]benzoate (**52**): mp 68–69 °C; IR (CH_2Cl_2) 1727, 1680, 1488, 1295, and 915 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.70 (s, 3H), 3.83 (s, 3H), 7.28 (t, 2H, J = 7.5 Hz), 7.38 (q, 2H, J = 7.2 Hz), 7.55-7.70 (m, 3H), and 7.88 (d, 1H, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 29.2, 51.5, 92.6, 93.1, 121.1, 122.7, 127.6, 127.8, 128.0, 129.9, 130.6, 131.0, 131.1, 133.3, 133.6, 165.5, and 199.1. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.67; H, 5.07. Found: C, 77.51; H, 4.93.

To a solution of 58 mg (1.41 mmol) of NaH (60%) in 10 mL of anhydrous THF was added a solution of 200 mg (0.72 mmol) of **52** in 10 mL of anhydrous THF under N_2. After heating at reflux for 4 h, the reaction mixture was poured over ice, acidified with a 10% solution of aqueous HCl, and extracted with ether. The combined ether extracts were washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. Chromatography of the residue on a silica gel column gave 180 mg (83%) of methyl 2-[2-[2-(1-oxoethyl)phenyl]-1-oxoethyl]benzoate (**55**): IR (CH_2Cl_2) 1716, 1688, 1273, 752, and 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.50 (s, 3H), 3.81 (s, 3H), 4.62 (s, 2H), 7.30–7.42 (m, 2H), 7.48–7.65 (m, 4H), 7.77 (d, 1H, J = 7.0 Hz), and 8.03 (d, 1H, J = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 28.4, 47.0, 41.8, 127.1, 127.6, 127.9, 129.5, 130.5, 130.8, 131.2, 132.3, 132.6, 136.2, 138.9, 139.8, 167.4, 201.1, and 201.2. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.95; H, 5.45. Found: C, 72.81; H, 5.28.

Reaction of Methyl 2-[2-[2-(1-Oxo-1-propyl)phenyl]-ethynyl]benzoate (53) with Sodium Hydride. To a solution containing 8.0 g (39.5 mmol) of 2-[2-(trimethylsilyl)ethynyl]-benzaldehyde in 150 mL of anhydrous THF was added dropwise at 0 °C 19.7 mL of a 3.0 M ethylmagnesium bromide solution. After stirring for 16 h at rt under N_2, the reaction mixture was poured over ice, acidified to neutral pH with a 10% aqueous HCl solution, and extracted with ether. The combined ether extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Chromatography of the residue on silica gel gave 3.21 g (44%) of 2-(1-hydroxypropyl)-1-[2-(trimethylsilyl)ethynyl]benzene: IR (neat) 2150, 1447, 1247, 854, and 757 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.25 (s, 9H), 0.97 (t, 3H, J = 8.0 Hz), 1.76 (m, 2H), 2.20 (d, 1H, J = 4.0 Hz), 5.05 (m, 1H), and 7.00–7.50 (m, 4H).

To a solution containing 3.50 g (15.1 mmol) of the above alcohol and 15.0 mL of water in 150 mL of THF was added 45 mL of a 1.0 M tetrabutylammonium fluoride solution at 0 °C. The mixture was stirred for 16 h, during which time it warmed to rt. The mixture was diluted with ether and washed successively with a saturated aqueous ammonium chloride solution, water, and brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 1.52 g (53%) of 2-(1-hydroxypropyl)-1-ethynylbenzene: IR (neat) 2100, 1445, 1047, and 759 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.93 (t, 3H, J = 7.0 Hz), 1.80 (qt, 2H, J = 7.0 Hz), 2.30 (bs, 1H), 3.30 (s, 3H), 5.10 (t, 1H), and 7.10–7.60 (m, 4H).

To a deaerated solution containing 1.28 g (8.0 mmol) of the above acetylene and 2.36 g (9.0 mmol) of methyl 2-iodobenzoate in 100 mL of distilled triethylamine were added 25 mg of bis(triphenylphosphine)palladium(II) chloride and 25 mg of CuI under an argon atmosphere. The mixture was heated at reflux for 16 h, cooled, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was chromatographed on silica gel to give 2.33 g (100%) of methyl 2-[2-[2-(1-hydroxy-1-propyl)phenyl]ethynyl]benzoate: IR (neat) 2210, 1719, 1297, 1255, and 758 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300

MHz) δ 1.00 (t, 3H, J = 7.4 Hz), 1.95 (m, 2H), 3.33 (d, 1H, J = 5.8 Hz), 3.93 (s, 3H), 5.05 (q, 1H, J = 6.1 Hz), 7.20–7.70 (m, 7H), 7.98 (d, 1H, J = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 10.5, 30.2, 52.3, 74.2, 92.6 (92.6), 120.7, 123.8, 126.1, 126.9, 127.8, 128.7, 130.4, 130.9, 131.8, 132.9, 134.0, 146.7, and 166.3.

To a solution of 2.42 g (11.0 mmol) of pyridinium chlorochromate in 50 mL of anhydrous CH_2Cl_2 was added a solution of 2.20 g (7.54 mmol) of the above alcohol in 20 mL of CH_2Cl_2 at rt under N_2. After stirring for 4 h, the mixture was poured into 50 mL of ether, and the remaining residue was washed with ether. The combined ether solution was concentrated under reduced pressure, and the residue was chromatographed on silica gel to give 1.54 g (71%) of methyl 2-[2-[2-(1-oxo-1-propyl)phenyl]ethynyl]benzoate (**53**): mp 62–63 °C; IR (neat) 2215, 1734, 1697, 1489, 790, and 761 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, 3H, J = 7.2 Hz), 3.18 (q, 2H, J = 7.2 Hz), 3.92 (s, 3H), 7.35–7.57 (m, 4H), 7.63–7.73 (m, 3H), and 7.97 (d, 1H, J = 7.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 8.3, 35.0, 52.0, 93.0, 93.1, 121.1, 123.2, 128.0, 128.1, 128.3, 130.3, 130.7, 131.5, 131.7, 133.9, 134.0, 140.8, 166.1, and 203.3. Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.05; H, 5.52. Found: C, 77.94; H, 5.46.

To a solution of 128 mg (5.33 mmol) of NaH (60%) in 15 mL of anhydrous THF was added a solution of 200 mg (0.68 mmol) of **53** in 15 mL of anhydrous THF under N_2. After heating at reflux for 4 h, the reaction mixture was poured over ice, acidified with 0.23 mL of a 10% solution of aqueous HCl, and extracted with ether. The combined ether extracts were washed with sodium bicarbonate, water, and brine, dried over magnesium sulfate, and concentrated under reduced pressure. Chromatography of the residue on silica gel gave 110 mg (60%) of methyl 2-(1-ethylidene-1*H*-2-benzopyran-3-yl)benzoate (**58**): IR (CH_2Cl_2) 1715, 1641, 1258, 725, and 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.00 (d, 3H, J = 7.2 Hz), 3.91 (s, 3H), 5.29 (q, 1H, J = 7.2 Hz), 7.15 (s, 1H), 7.22 (t, 1H, J = 7.7 Hz), 7.30–7.40 (m, 2H), 7.46 (t, 1H, J = 3.5 Hz), 7.54 (t, 1H, J = 7.2 Hz), 7.67 (t, 1H, J = 4.3 Hz), 7.93 (d, 1H, J = 8.1 Hz), and 8.42 (d, 1H, J = 8.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 10.9, 51.9, 94.5, 95.3, 119.2, 120.2, 125.2, 127.6, 128.4, 129.1, 129.8, 130.6, 131.7, 132.9, 134.3, 136.2, 152.6, 152.9, and 168.2. Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.05; H, 5.52. Found: C, 77.86; H, 5.31.

A 50 mg (0.17 mmol) sample of **58** in 2 mL of aqueous acetone containing a drop of sulfuric acid was allowed to stir at 25 °C for 3 h. Standard workup followed by thick layer chromatography furnished 40 mg (80%) of ketone **56**: IR (CH_2Cl_2) 1715, 1685, 1275, and 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, J = 7.1 Hz), 3.15 (q, 2H, J = 7.1 Hz), 3.85 (s, 3H), 4.60 (s, 2H), and 7.25–7.95 (m, 8H).

Reaction of Methyl 2-[2-[2-(1-Oxo-5-hexenyl)phenyl]-ethynyl]benzoate (54) with Sodium Hydride. To a stirred solution of 600 mg (24.7 mmol) of activated magnesium turnings in 30 mL of anhydrous ether was added 2.52 g (16.9 mmol) of 5-bromo-1-pentene at a rate sufficient to maintain gentle reflux under N_2. The reaction mixture was stirred for 15 min at rt after the addition was complete. The Grignard solution was added dropwise, over 10 min, to a solution of 2.85 g (14.1 mmol) of 2-[2-(trimethylsilyl)ethynyl]benzaldehyde in 30 mL of anhydrous ether at 0 °C under N_2. The ice bath was removed and the reaction mixture stirred for 1 h at rt. The mixture was poured over ice and acidified with 10% HCl. The layers were separated, and the aqueous layer was washed with 30 mL of ether. The combined ether layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Chromatography of the resulting residue on silica gel gave 3.19 g of 2-(1-hydroxy-5-hexenyl)-1-[2-(trimethylsilyl)ethynyl]benzene: IR (neat) 2160, 1250, 1065, 870, and 765 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.25 (s, 9H), 1.00–1.65 (m, 4H), 1.70–2.00 (m, 2H), 2.10 (bs, 1H), 4.60–5.00 (m, 4H), and 6.85–7.35 (m, 4H).

To a solution of 323 mg (0.15 mmol) of pyridinium chlorochromate in 2 mL of anhydrous CH_2Cl_2 was added 270 mg (0.99 mmol) of 2-(1-hydroxy-5-hexenyl)-1-[2-(trimethylsilyl)-ethynyl]benzene in 0.2 mL of anhydrous CH_2Cl_2. The mixture was stirred at rt for 2 h, after which 10 mL of ether was added. The solvent was decanted from the black residue, and the mixture was chromatographed on silica gel to give 251 mg (93%) of 2-(1-oxo-5-hexen-1-yl)-1-(trimethylsilyl)benzene: IR (neat) 2160, 1690, 1440, 870, and 770 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 0.30 (m, 9H), 1.70–2.30 (m, 4H), 3.13 (t, 2H, J = 6.0 Hz), 4.90–5.20 (m, 2H), 5.60–6.16 (m, 1H), and 7.30–7.70 (m, 4H).

To a solution containing 500 mg (1.85 mmol) of the above ketone and 0.5 mL of water in 20 mL of THF was added 5.5 mL of a 1.0 M tetrabutylammonium fluoride solution at 0 °C. The mixture was stirred for 24 h, during which time it warmed to rt. The reaction mixture was diluted with ether and washed successively with a saturated aqueous ammonium chloride solution, water, and brine. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 310 mg (85%) of 2-[2-(1-oxo-5-hexenyl)ethynyl]benzene: IR (neat) 2120, 1695, 1000, 920, and 770 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.70–2.30 (m, 4H), 3.1 (t, 2H, J = 6.0 Hz), 3.40 (s, 1H), 4.90–5.20 (m, 2H), 5.60–6.10 (m, 1H), and 7.30–7.70 (m, 4H).

To a deaerated solution containing 2.67 g (10.2 mmol) of methyl 2-iodobenzoate and 2.16 g (10.9 mmol) of the above acetylene in 75 mL of triethylamine were added 30 mg of bis-(triphenylphosphine)palladium(II) chloride and 60 mg of CuI under Ar. The mixture was heated at 60 °C for 16 h, cooled, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was chromatographed on silica gel to give 4.22 g (91%) of methyl 2-[2-[2-(1-oxo-5-hexenyl)phenyl]ethynyl]benzoate (**54**): IR (neat) 1735, 1695, 1305, 1090, and 770 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.84 (tt, 2H, J = 7.4 and 7.3 Hz), 2.12 (dt, 2H, J = 7.3 and 7.1 Hz), 3.18 (t, 2H, J = 7.4 Hz), 3.94 (s, 3H), 4.91 (d, 1H, J = 10.6 Hz), 4.99 (d, 1H, J = 17.5 Hz), 5.76 (ddt, 1H, J = 17.5, 10.6, and 7.1 Hz), 7.35–7.55 (m, 4H), 7.63–7.72 (m, 3H), and 8.00 (d, 1H, 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.3, 33.0, 41.1, 52.1, 93.0, 93.2, 115.0, 121.1, 123.3, 128.0, 128.2, 128.4, 130.4, 130.8, 131.5, 131.7, 133.9, 134.0, 137.9, 141.0, 166.1, and 202.8.

To a solution of 48 mg (1.2 mmol) of sodium hydride (60%) in 15 mL of anhydrous THF was added a solution of 200 mg (0.6 mmol) of **54** in 15 mL of anhydrous THF under N_2. After heating at reflux for 4 h, the reaction mixture was poured over ice, acidified with a 10% solution of aqueous HCl, and extracted with ether. The combined ether extracts were washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. Chromatography of the residue on silica gel afforded 110 mg (52%) of methyl 2-[2-(2-[1-oxohexenyl)phenyl]-1-oxoethyl]benzoate (**57**): IR (CH_2Cl_2) 1715, 1690, 1272, and 762 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.80 (qt, 2H, J = 7.4 Hz), 2.10 (dt, 2H, J = 7.4 and 7.0 Hz), 2.79 (t, 2H, J = 7.4 Hz), 3.80 (s, 3H), 4.60 (s, 2H), 4.95 (d, 1H, J = 10.3 Hz), 5.00 (d, 1H, J = 16.9 Hz), 5.76 (ddt, 1H, J = 16.9, 10.3, and 7.0 Hz), 7.30–7.40 (m, 2H), 7.50–7.60 (m, 4H), 7.80–7.87 (m, 1H), and 8.05–8.13 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.1, 32.9, 40.2, 46.8, 51.8, 115.0, 127.1, 127.3, 127.9, 129.4, 130.6, 130.7, 130.8, 132.4, 132.6, 136.3, 137.9, 139.2, 139.8, 167.3, 200.4, and 204.1. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.40; H, 6.33. Found: C, 75.27; H, 6.19.

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Supporting Information Available: ^{1}H-NMR and ^{13}C-NMR spectra for isobenzofuran **42** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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