Hydroxyacetals, phthalans, and isobenzofurans therefrom

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A general method for the generation of isobenzofuran intermediates is described. Lithiated aromatic acetals are converted to hydroxyacetals (A) which may be cyclized to isobenzofurans by mild acid treatment through the 1-hydroxyphthalans (B). The isobenzofurans generated *in situ* are trapped by a variety of dienophiles to provide the expected oxo-bicyclo adducts (C). The mass and ^{1}Hmr spectra of B and C are discussed.

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On décrit une méthode générale de production des intermédiaires de l'isobenzofuranne. On transforme les acétals aromatiques lithiés en hydroxyacétals (A) que l'on peut cycliser en isobenzofurannes via les hydroxy-1 phtalanes (B) en présence d'un acide dans des conditions douces. On piège les isobenzofurannes générés *in situ* avec divers diénophiles pour obtenir les adduits oxo-bicyclo attendus (C). On discute des spectres de masse et de rmn du ^{1}H des composés B et C.
[Traduit par le journal]

The benzo[*c*]furan system, trivially called isobenzofuran (ISB), has been known (1) since 1964. In the following years, many methods were developed for the production of isobenzofurans, most of them involving retro Diels–Alder reactions of various precursors (2) and culminating in the isolation (3) of the parent benzo[*c*]furan as an unstable solid very prone to polymerization. Several theoretical calculations (2) suggest that the molecule is nonaromatic but the appearance of furanoid protons at δ 8.40 in the ^{1}Hmr spectrum of ISB implies (3) the presence of a significant ring current. The reactivity of isobenzofurans as dienes in the Diels–Alder reaction, however, is extremely well documented (2) and their widespread application[1] to the construction of aromatic and hydroaromatic natural products has hitherto been limited only by the lack of versatile methods of ISB synthesis. Syntheses not entailing Diels–Alder reversions have been reported (5) in recent years and the consequent enhancement in synthetic versatility has led to many applications of inter (6) and intramolecular (7) Diels–Alder reactions of ISB's in natural product synthesis. In this report we discuss some of our recent work on the generation of a variety of ISB's and their reactions with many common dienophiles.

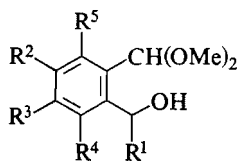
The aromatic acetal route we have employed is generalized in Scheme 1. It is a "one-pot" process, although phthalans (B) and even isobenzofurans[2] may be isolated in some instances.

Preparation of hydroxyacetals (A)

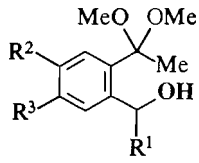
Many acetals (and ketals), incorporating a variety of substituents differing in number, type, and position, were prepared. The most convenient route, also the simplest, begins with a bromoaldehyde which is converted to its dimethyl acetal (with trimethylorthoformate and Dowex 50 W-X2 resin in refluxing methanol), lithiated by halogen–lithium exchange, and reacted with formaldehyde or an aromatic aldehyde (**A1**–**A5**).

Alternatively, direct *ortho*-deprotonation (8) of aromatic acetals, followed by treatment of the ensuing *ortho*-lithio species with nonenolizable aldehydes, provides a series of contiguously substituted hydroxyacetals (**A6**–**A8**). A major shortcoming of these preparations is that the aryl lithium species is readily protonated by enolizable aldehydes or ketones, thus precluding the use of most aliphatic aldehydes and limiting the R^1 substituent to H or aryl.

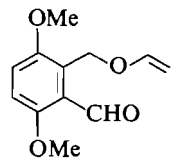
One solution to this problem is to start with a bromoketal instead, and to carry out the same sequence of reactions. Thus, hydroxyketals **A9**–**A11** are obtained by halogen–lithium exchange from the corresponding bromoketal and reaction with formaldehyde (**A9**, **A10**) or piperonal (**A11**). Compounds **A9** and **A10** are precursors of 1-methyl isobenzofurans and in general this route will provide 1,3-dialkyl (or 1,3-alkyl aryl)



A1 $R^2 = R^3 = OMe$, R^1 = 3,4-methylenedioxyphenyl, $R^4 = R^5 = H$
A2 $R^2 + R^3 = OCH_2O$, R^1 = 3,4-methylenedioxyphenyl, $R^4 = R^5 = H$
A3 $R^2 + R^3 = OCH_2O$, R^1 = 3,4-dimethoxyphenyl, $R^4 = R^5 = H$
A4 $R^2 + R^3 = OCH_2O$, R^1 = 3,4,5-trimethoxyphenyl, $R^4 = R^5 = H$
A5 $R^2 = R^3 = OMe$, $R^1 = R^4 = R^5 = H$
A6 $R^3 = R^4 = OMe$, R^1 = 3,4-methylenedioxyphenyl, $R^2 = R^5 = H$
A7 $R^2 = R^3 = R^4 = OMe$, R^1 = 3,4,5-trimethoxyphenyl, $R^5 = H$
A8 $R^3 = R^4 = OMe$, $R^1 = R^2 = R^5 = H$
A12 $R^2 + R^3 = OCH_2O$, $R^4 = R^5 = H$, R^1 = cyclohexyl

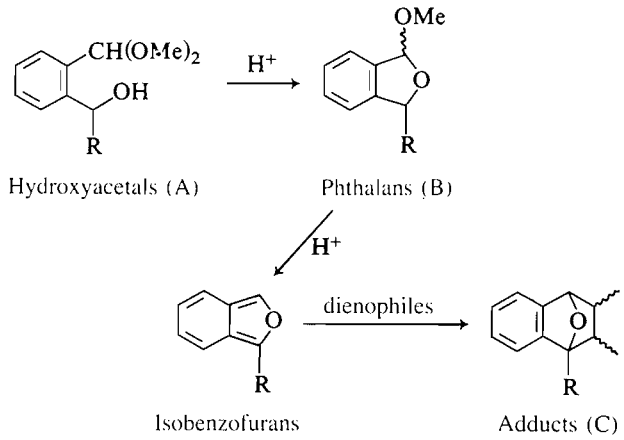


A9 $R^2 = R^3 = OMe$, $R^1 = H$
A10 $R^2 + R^3 = OCH_2O$, $R^1 = H$
A11 $R^2 = R^3 = OMe$, R^1 = 3,4-methylenedioxyphenyl



A13

[1]One exception has been the use of an isobenzofuran intermediate in the synthesis of an anthracyclinone (see ref. 4).
[2]D. Rajapaksa and R. Rodrigo. Unpublished results.



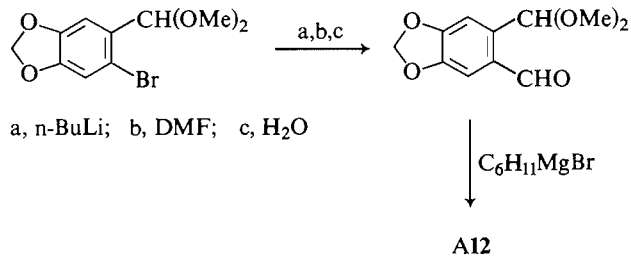
SCHEME 1

isobenzofurans.

In the course of our work we have made the fortuitous discovery that carbinolamines arising from the capture of lithiated acetals by dimethyl formamide can be selectively hydrolysed without affecting the acetal moiety to provide *ortho* formyl acetals. Thus hydroxyacetal **A12** was prepared from the 6-bromo dimethyl acetal of piperonal as illustrated in Scheme 2.

The success of this Grignard route provides another avenue of access to such hydroxyacetals (R^1 = alkyl) previously prepared by the ketal method. Furthermore, the potential of the Grignard and bromoketal technologies for assembling complex fragments, in preparation for intramolecular Diels–Alder reactions, is obvious. Investigations concerned with the synthesis of condensed hydroaromatic systems by these methods are in progress.

All but two (**A4** and **A8**) of these hydroxyacetals are oils that



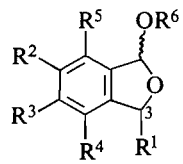
SCHEME 2

provided spectroscopic data consistent with their structures but resisted crystallization. They were used without further purification for the generation of isobenzofurans according to Scheme 1.

The mass spectra of these compounds are characterized by the presence of prominent ions resulting from sequential elimination of two molecules of methanol from the parent ion ($M - 32$, $M - 64$); an ion corresponding to loss of methanol and a methoxy radical ($M - 63$) is also found in the spectra.

Phthalans (B)

The 1-methoxy (or hydroxy) phthalans formed by mild acid treatment of the hydroxyacetals are easily detectable by ^{1}Hmr spectroscopy. Some were isolated and characterized (**B2**, **B5**, **B6**, **B7**, **B8**, **B13**, and **B14**). The known 1-hydroxyphthalan **B14** was prepared by reduction of the corresponding phthalide as previously reported (9). This is not a general route to hydroxyphthalans, however; its success depends on the presence of "peri" substituents (R4, R5 ≠ H) in the benzene ring. They prevent the ring opening and thereby forestall the further reduction of the masked aldehyde initially formed. A similar explanation has been advanced (10) for reactions where one mole of a Grignard reagent adds to certain peri-substituted phthalides to form hydroxyphthalans. The related 1-methoxyphthalan

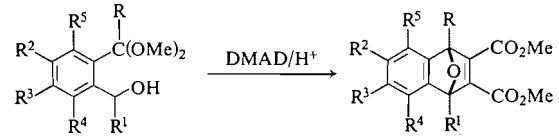


B2 $R^2 + R^3 = OCH_2O$, R^1 = 3,4-methylenedioxyphenyl, $R^4 = R^5 = R^6 = H$
B5 $R^2 = R^3 = OCH_3$, $R^1 = R^4 = R^5 = H$, R^6 = Me
B6 $R^3 + R^4 = OCH_2O$, R^1 = 3,4-methylenedioxyphenyl, $R^2 = R^5 = H$, R^6 = Me
B7 $R^2 = R^3 = R^4$ = OMe, R^1 = 3,4,5-trimethoxyphenyl, $R^5 = H$, R^6 = Me
B8 $R^3 = R^4$ = OMe, $R^1 = R^2 = R^5 = H$, R^6 = Me
B13 $R^4 = R^5$ = OMe, $R^1 = R^2 = R^3 = H$, R^6 = Me
B14 $R^4 = R^5$ = OMe, $R^1 = R^2 = R^3 = R^6 = H$

B13 was also prepared by a more direct route from 2,5-dimethoxybenzyl alcohol. Lithiation (11) of its vinyl ether and treatment and dimethylformamide provided a hydroxyacetal equivalent **A13** which, upon successive treatment with methanolic mercuric acetate and methanolic *p*-toluene sulfonic acid, gave **B13**.

Phthalans show substantial long-range coupling between protons at C-1 and C-3. It has been suggested that this is a "dual pathway" interaction ($^4J + {}^3J$) and its magnitude in several variants of 2,5-dihydrofurans has been related (12) to conformational factors. Our phthalans all possess a C-1 oxygen substituent and in every instance we have observed that $J_{1,3}$ (*trans*) is ≈2.4 Hz while $J_{1,3}$ (*cis*) ≈ 0 Hz. Although such a distinct stereochemical dependence of 1,3 coupling has not been previously reported for oxygen-substituted phthalans, similar drastic decreases in the 1,3 *cis* coupling constants of 2,5-dihydrofurans have been noted and correlated (12) with the electronic effects of a 2-oxygen substituent in the latter compounds. It thus appears that in 1- or 3-oxygenated phthalans the magnitude of the long-range ($J_{1,3}$) coupling is stereochemically diagnostic. In all our phthalans where *cis* and *trans* stereoisomers can exist we find that ring closure of the acyclic precursors takes place approximately equally in either direction to produce a 1:1 mixture of *cis* and *trans* isomers. Signals of H-1 and H-3 of both isomers are visible in the ^{1}Hmr spectrum in approximately equal intensities. The isomers must be of about

TABLE 1. Reactions of hydroxy acetals* with dimethylacetylene dicarboxylate



Hydroxy acetal	Adduct (yield, %)
A**1**	C**1**(65)
A**2**	C**2**(65)
A**3**	D**3**(62)†
A**4**	C**4**(65)
A**5**	C**5**(99)
A**6**	D**6**(62)†
A**7**	D**7**(73)†
A**8**	C**8**(34)
A**9**	C**9**(96)
A**10**	C**10**(96)
A**11**	C**11**(96)
A**12**	C**12**(70)

*R = H except in A**9**, C**9**–A**11**, C**11** (R = Me).
†Isolated as the naphthol.

equal stability because the 1 : 1 proportion is unaffected by the duration of acid exposure in the cyclization.

The Diels–Alder reaction and formation of adducts (C)

The Diels–Alder reactions of ISB precursors A and B were studied in two ways. In the first instance almost all precursors were reacted with dimethyl acetylenedicarboxylate in the presence of a catalytic quantity of glacial acetic acid at steam bath temperatures. With this combination of reactants both regiochemical and stereochemical problems were avoided for the time being. The bridged adducts were isolated in good yields after crystallization from ether. In a few cases care had to be taken to prevent aromatization to the naphthol. Thus adducts **C1**, **C2**, and **C4** (Table 1) were very prone to aromatization and careful control of time (25–30 min) and temperature (95–100°C) was necessary. Under these conditions the Diels–Alder reaction remains incomplete and acceptable yields of these compounds were only obtained after recycling mother liquors remaining from crystallization of the adducts. Adducts **C3** and **C10** resisted crystallization but could be converted to the crystalline naphthols **D3** and **D10** by further acid treatment. Adduct **C7** could not be obtained under any conditions. It appears that the peri-methoxy group (R_4 = OMe) hinders ISB formation below 130°C. At this temperature **C7** is rapidly isomerized to **D7**, the isolated product.

In a second study, a symmetrical ISB precursor **A5** (or **B5**) was subjected to Diels–Alder additions with a variety of dienophiles (Table 2). Regiochemical complications were thus circumvented but in every case mixtures of *endo–exo* products were isolated in good to excellent yields. *endo* Isomers generally predominated except in the case of the 2-butenolide adduct (entry 4). *endo* Isomers were crystallized from the mixture in some cases (entries 2, 5, and 8) while in others the adducts were separated by a combination of chromatography and fractional crystallization. *endo–exo* Ratios were easily estimated by ^{1}Hmr spectroscopy, aided by spectra of pure isomers where available. To illustrate the use of ^{1}Hmr spectroscopy for this purpose, a tabulation and brief discussion of the spectra of pure *exo* and *endo* **C5***i* (entry 9, Table 2) is presented below (Table 3).

Differences between the spectra of *exo* and *endo* isomers observed here are typical of all the adducts and are easily detected and explained. In the *exo* isomers bridgehead protons (H-1) are singlets; H-4 is coupled only to the β-proton at C-3 and thus appears as a doublet in both isomers. These protons are rigidly held in a plane approximating that of the adjacent benzene ring and are consequently subject to its deshielding influence. Thus H-1 and H-4 signals are both around δ 5.5 but with differing coupling patterns in the two isomers. No "phthalan-type" long range coupling was found between these two protons, however, even though the rigidity of the molecule ensures a favourable "W" pathway. Further differences between the two spectra can also be associated with the disposition of the C-2 substituent. A significant variation is found in H-9 (aldehyde proton) and H-2 resonances, an obvious consequence of differential shielding by the benzene ring. Such shielding also affects the 3α protons in both isomers making $\Delta\nu(3\alpha,3\beta)$ relatively large and thus simplifying the spectra. Slight, but consistent, differences in the absorptions of aromatic protons and substituents between *exo* and *endo* isomers are seen in all adducts. Again, it is the C-2 substituent in the *endo* configuration only that is responsible for the nonequivalence of the observed chemical shifts. All assignments and coupling constants were secured by decoupling experiments and 400 MHz spectra where necessary.

The mass spectra of all adducts were characterized by the presence of a very intense ion corresponding to a retro Diels–Alder fission of the molecular ion. This ion, the base peak in all spectra, corresponds to 5,6-dimethoxy isobenzofuran. Charge localization on the "dienophile" is also observed in many cases. The ISB ion (common at *m/z* 178 in all examples of **C5**) shows subsequent extrusions of CO, CH_3, CO, and CH_2O represented by ions at 150, 135, 107, and 77 mass units respectively. A minor decomposition pathway in all **C5** cases (except **C5***f*) involves dehydration to a naphthalene represented by an ion at $M - 18$ ($M - 19$ in 2-deutero examples).

Adducts substituted at a bridgehead position by an aryl group (e.g. **C1**–**C4**, **C6**, **C7**) were easily aromatized to the corresponding naphthols (6, 7).

Experimental

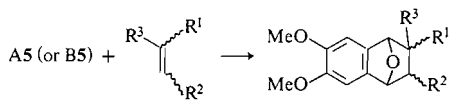
General methods

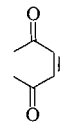
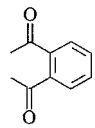
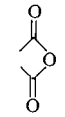
Melting point determinations were made using a Buchi SMP-20 apparatus and are uncorrected. Infrared spectra were obtained on Beckman Model IR-10 or on Acculab 10 spectrophotometers. Nuclear magnetic resonance spectra were obtained on either a Varian T-60, Perkin–Elmer R12-B, Bruker WP-80, or Bruker WH-400 spectrophotometer. Samples were run in $CDCl_3$ solutions containing tetramethylsilane as an internal standard. Low and high resolution mass spectra were measured on a Varian VG Organic 7070F mass spectrometer. Flash column chromatography was performed using Merck 0.063–0.200 mm (70–230 mesh) silica gel 60 which was packed dry into glass columns and eluted with benzene–acetone (4:1) unless otherwise noted. Combustion analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario and/or Canadian Microanalytical Service Ltd, Vancouver, British Columbia.

General method for preparing benzaldehydedimethyl acetals

A stirred mixture of the benzaldehyde (0.1 mol), trimethylorthoformate (0.3 mol), absolute methanol (150 mL), and Dowex 50W-X8 acid exchange resin was refluxed for 20 h. The solution was cooled, filtered, and evporated *in vacuo*. The residual oil was distilled *in vacuo* providing the acetal in pure form.

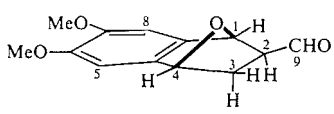
TABLE 2. Reaction of A5 (and B5) with dienophiles

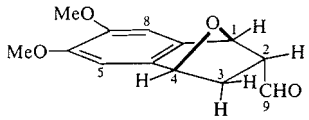


Dienophile	Yield (*endo: exo*)	Adduct (C)	
1. Benzoquinone	60(7:3)	$R^1 + R^2 =$  , $R^3 = H$	C5a
2. Naphthoquinone	86(3:1)*	$R^1 + R^2 =$  , $R^3 = H$	C5b
3. Methyl vinylketone	80(3:2)†	$R^1 =$ COMe, $R^2 = R^3 = H$	C5c
4. 2-Butenolide	72(1:2)†	$R^1 + R^2 =$  , $R^3 = H$	C5d
5. Acrylonitrile	64(9:1)*	$R^1 =$ CN, $R^2 = R^3 = H$	C5e
6. α-Chloroacrylonitrile	70	$R^1 =$ CN, $R^3 =$ Cl, $R^2 = H$	C5f
7. Maleic anhydride	60(7:3)	$R^1 + R^2 =$  , $R^3 = H$	C5g
8. Methyl acrylate	50(3:2)	$R^1 = CO_2Me$, $R^2 = R^3 = H$	C5h
9. Acrolein	63(3:2)†	$R^1 =$ CHO, $R^2 = R^3 = H$	C5i

**endo* Adduct crystallized.
†Adducts separated and crystallized.

TABLE 3.





	exo			*endo*		
Proton	δ(ppm)	Multiplicity	*J* (Hz)	δ(ppm)	Multiplicity	*J* (Hz)
1	5.57	s		5.51	d	1,2 = 5.08
2	2.49	ddd	2,9 = 3.06 2,3α = 8.55 2,3β = 3.66	3.23	dddd	1,2 = 5.08 2,9 = 3.32 2,3α = 3.71 2,3β = 9.50
3α	1.67	dd	*gem* = 11.6 2,3α = 8.55	1.67	dd	*gem* = 11.8 2,3α = 3.71
3β	2.36	ddd	2,3β = 3.66 *gem* = 11.6 3β,4 = 4.88	2.35	ddd	2,3β = 9.5 *gem* = 11.8 3β,4 = 5.08
4	5.49	d	3β,4 = 4.88	5.45	d	3β,4 = 5.08
9	9.74	d	2,9 = 3.05	8.91	d	2,9 = 3.32
5,8	6.90	s		6.84,6.91	s, s	
2 × OMe	3.88	s		3.85, 3.88	s, s	

General lithium–halogen exchange procedure (A1–A5, A9–A11)

A stirred solution of the bromoacetal and dry diethyl ether (15 mL) was cooled to −78°C under N_2. n-BuLi (1.1 equiv./ mol of acetal) was added dropwise and the resulting precipitate stirred for 0.5 h before being treated with the appropriate electrophilic reagent. Increasing the scale of the reaction to 30 mmol did not noticeably affect the yields.

6-Formyl piperonal dimethyl acetal

6-Bromopiperonal dimethyl acetal (6.08 g, 22.1 mmol) was lithiated as previously described and treated with excess of dry dimethylformamide (10 g, 137 mmol) at −78°C. The reaction mixture was allowed to warm up to room temperature during 2 h and quenched with H_2O. The ether layer was separated, the aqueous layer extracted with ether (2 × 50 mL), and the combined ether extracts washed with

a saturated solution of NaCl and dried (Na_2SO_4). Evaporation of solvent gave crystalline 6-formyl piperonal dimethylacetal (4.05 g, 82%) which was recrystallized from ether–hexane, mp 80°C; ir ($CHCl_3$): 1670 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ 3.40 (s, 6H, 2 OMe), 5.85 (s, 1H, C*H*(OMe)$_2$), 6.08 (s, 2H, OCH_2O), 7.18, 7.40 (s, 1H each, Ar), 10.30 (s, 1H, CHO); mass spectrum, *m/z* (assignment): 224 (M^+), 209 ($M^+ - CH_3$) 194 ($M^+ - 2\ CH_3$), 193 ($M^+ - OCH_3$). *Anal.* calcd. for $C_{11}H_{12}O_5$: C 58.92, H 5.35; found: C 58.96, H 5.26.

*Compound A***1**

6-Bromo-3,4-dimethoxybenzaldehyde dimethyl acetal (5.0 g, 17.2 mmol) was lithiated as previously described. To the stirred suspension was added a solution of piperonal (2.8 g, 18.7 mmol) and dry diethyl ether (50 mL) via a pressure-equalizing dropping funnel. The mixture was stirred for 0.5 h, poured into H_2O (50 mL), and extracted with ether (2 × 50 mL). The extract was dried (Na_2SO_4) and evaporated *in vacuo*. This afforded a light oil (16.6 g, 95%) which was not purified further; ir (neat): 3450 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz), δ: 3.23 (s, 6H, —CH(OC*H*$_3$)$_2$), 3.37 (d, 1H, —OH, *J* = 4 Hz, exchangeable with D_2O), 3.85, 4.18 (s, 3H each, 2 × OCH_3), 5.40 (s, 1H, C*H*(OCH$_3$)$_2$), 5.87 (s, 2H, —OCH_2O—), 5.97 (d, 1H, —C*H*OH, *J* = 4 Hz, collapses to a singlet after D_2O), 6.63–6.90 (m, 4H, Ar), 7.05 (s, 1H, Ar); mass spectrum, *m/z* (assignment): 362 (M^+), 330 ($M^+ - CH_3OH$), 299 ($M^+ - CH_3OH - CH_3O$), 298 ($M^+ - 2CH_3OH$).

*Compound A***2**

6-Bromo-3,4-methylenedioxybenzaldehydedimethyl acetal (5.0 g, 18.2 mmol) was lithiated and treated with piperonal (2.87 g, 19.1 mmol) as previously described. Work-up was similar to that of A**1** and afforded an oil (6.0 g, 95%) which was not purified further; ir (neat): 3420 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz) δ: 3.21 (s, 6H, 2 × OCH_3), 3.45 (br, 1H, OH, exchangeable with D_2O), 5.37 (s, 1H, C*H*(OCH$_3$)$_2$), 5.87 (s, 4H, 2 × —OCH_2O—), 5.96 (br, 1H, —C*H*OH, sharpens with D_2O,) 6.66–6.95 (m, 3H, Ar), 6.75, 7.02 (s, 1H, each, Ar); mass spectrum, *m/z* (assignment): 346 (M^+), 314 ($M^+ - CH_3OH$), 283 ($M^+ - CH_3OH - CH_3O$), 282 ($M^+ - 2CH_3OH$).

*Compound A***3**

6-Bromo-3,4-methylenedioxybenzaldehydedimethyl acetal (5.0 g, 18.2 mmol) was lithiated and treated with veratraldehyde (3.15 g, 1.90 mmol). Work-up as described gave A**3** as an oil (6.0 g, 91%) which was not purified further; ir (neat): 3520 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz), δ: 3.25 (s, 6H, CH(OC*H*$_3$)$_2$), 3.50 (d, 1H, OH, *J* = 4.2 Hz, disappears with D_2O), 3.91 (s, 6H, 2 × OCH_3), 5.42 (s, 1H, C*H*(OCH$_3$)$_2$, 5.95 (s, 2H, —OCH_2O—), 6.1 (d, 1H, *J* = 4.2 Hz, collapses to a singlet with D_2O), 6.7–7.2 (m, 5H, Ar); mass spectrum, *m/z* (assignment): 362 (M^+), 330 ($M^+ - CH_3OH$), 299 ($M^+ - CH_3OH - CH_3O$), 298 ($M^+ - 2CH_3OH$).

*Compound A***4**

Treatment of lithiated 6-bromo-3,4-methylenedioxybenzaldehydedimethyl acetal (3.0 g, 10.9 mmol) with 3,4,5-trimethoxybenzaldehyde (2.3 g, 11.7 mmol) gave A**4** as an oil (4.0 g, 93%) which later crystallized from diethyl ether; mp 111–112.5°C; ^{1}Hmr ($CDCl_3$, 60 MHz), δ: 3.22, 3.30 (s, 3H each, CH(OC*H*$_3$)$_2$), 3.77 (s, 9H, —OCH_3), 3.6 (d, 1H, OH, disappears with D_2O), 5.41 (s, 1H, —C*H*(OCH$_3$)$_2$), 5.80 (s, 2H, —OCH_2O—), 6.01 (d, 1H, —C*H*OH, collapses to a singlet with D_2O), 6.55 (s, 2H, Ar), 6.63, 6.95 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 392 (M^+), 360 ($M^+ - CH_3OH$), 329 ($M^+ - CH_3OH - CH_3O$), 328 ($M^+ - 2CH_3OH$); hrms calcd. for $C_{20}H_{24}O_8$: 392.1471; found: 392.1414. *Anal.* calcd. for $C_{20}H_{24}O_8$: C 61.21, H 6.17; found: C 61.01, H 6.41.

*Compound A***5**

6-Bromo-3,4-dimethoxybenzaldehydedimethyl acetal (5.4 g) was lithiated and treated with anhydrous formaldehyde gas. The latter was generated by pyrolyzing paraformaldehyde (6 g) with a hot air gun and the resulting gas passed, in a stream of drynitrogen, over a boat of anhydrous $CaCl_2$ and into the lithiated solution. The mixture was stirred for 1 h at room temperature and poured into H_2O (50 mL). The ether layer was separated, dried (Na_2SO_4), and the ether removed *in vacuo* to leave an oil (95%) which resisted crystallization; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 3.01 (t, 1, OH, disappears with D_2O), 3.35 (s, 6H, —CH(OC*H*$_3$)$_2$, 3.85 (s, 6H, 2 × OCH_3), 4.59 (d, 2H, O—C*H*$_2$OH, collapses to a singlet in D_2O), 5.41 (s, 1H, —C*H*(OCH$_3$)$_2$), 6.82, 7.00 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 242 (M^+), 210 ($M^+ - CH_3OH$).

*Compound A***7**

2-Bromo-3,4,5-trimethoxybenzaldehydedimethyl acetal (1.46 g, 4.5 mmol) was lithiated and previously described. To the stirred suspension was added a solution of 3,4,5-trimethoxybenzaldehyde (0.891 g, 4.56 mmol) in dry ether (50 mL). Work-up as previously described gave A**7** as an oil (1.9 g, 95.6%), ir (neat): 3450 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.27, 3.29, 3.50, 3.74, 3.79, 3.80, 3.81, 3.83 (all s, 3H each, 8 OMe groups), 3.98 (d, 1H, OH, exchangeable with D_2O), 5.30 (s, 1H, C*H*(OMe)$_2$), 6.1 (d, 1H, C*H*OH, *J* = 10.7 Hz), 6.55, 6.56, 6.96 (all s, 1H each, Ar), mass spectrum, *m/z* (assignment): 438 (M^+), 406 ($M^+ - CH_3OH$), 375 ($M^+ - CH_3OH - CH_3O$), 374 ($M^+ - 2CH_3OH$).

General lithiation procedure for piperonal and veratraldehyde dimethyl acetals

A stirred solution of the acetal and dry diethyl ether (15 mL), under N_2, was cooled to 0°C and treated with n-BuLi (1.1 equiv./mole of acetal). After 1 h the mixture was treated with the appropriate electrophilic reagent.

*Compound A***6**

Veratraldehyde dimethyl acetal (2.07 g; 9.76 mmol) was lithiated and treated dropwise with an ethereal solution of piperonal (1.46 g, 9.8 mmol in 50 mL) at −78°C. It was allowed to warm up to room temperature. Work-up similar to that of A**1** afforded an oil (3.35 g, 95%) which was used in the Diels–Alder reaction without further purification; ir (neat): 3450 (OH) cm^{-1}; Hmr ($CDCl_3$, 80 MHz), δ: 3.23 (s, 6H, 2 acetal OCH_3), 3.52 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.2 (d, 1H, OH, *J* = 10 Hz, exchangeable with D_2O), 5.2 (s, 1H, C*H*(OMe)$_2$), 5.85 (s, 2H, —OCH_2O), 6.13 (d, 1H, C*H*OH, *J* = 10 Hz), 6.65–7.35 (m, 5H, Ar); mass spectrum, *m/z* (assignment): 362 (M^+), 331 ($M^+ - CH_3O$), 330 ($M^+ - CH_3OH$), 299 ($M^+ - CH_3OH - CH_3O$), 298 ($M^+ - 2CH_3OH$).

*Compound A***8**

Veratraldehyde dimethyl acetal (2.5 g) was lithiated and treated with gaseous formaldehyde as per A**5**. Similar work-up gave a white amorphous solid which later crystallized from ether (2.7 g, 95%); mp 54–56°C; ir ($CHCl_3$): 3420 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz), δ: 3.0 (t, 1H, OH, disappears with D_2O), 3.35 (s, 6H, —CH(OCH_3)$_2$), 3.81 (s, 6H, 2 × OCH_3), 4.70 (d, 2H, C*H*$_2$OH), collapses to a singlet with D_2O), 5.32 (s, 1H, —CH(OCH$_3$)$_2$), 6.65 and 7.07 (ABq, 1H each, J_{ortho} = 8.1 Hz, Ar); mass spectrum, *m/z* (assignment): 242 (M^+), 210 ($M^+ - CH_3OH$). *Anal.* calcd. for $C_{12}H_{18}O_5$: C 59.49, H 7.49; found: C 59.22, H 7.78.

*Compound A***9**

6-Bromo-3,4-dimethoxyacetophenonedimethyl ketal (2.0 g) was lithiated and treated with formaldehyde gas (6 g of paraformaldehyde) as previously described. Similar work-up afforded an oil (86%) which resisted crystallization; ir (neat): 3450 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 1.60 (s, 3H,—CH_3), 3.2 (s, 1 1H, OH, disappears with D_2O), 3.29 (s, 6H, —C(OCH$_3$)$_2$)CH$_3$), 3.90 (s, 6H, 2 × OCH_3), 4.61 (s, 2H, —C*H*$_2$O), 6.93, 7.07 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 256 (M^+), 225 ($M^+ - CH_3O$).

*Compound A***10**

6-Bromo-3,4-methylenedioxyacetophenonedimethyl ketal (1 g) was lithiated and treated with formaldehyde gas (3 g of paraformaldehyde) as previously described. Similar work-up gave an oil (72%) which resisted crystallization; ir (neat): 3460 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 1.58 (s, 3H,—CH_3), 3.0 (t, 1H, —OH, disappears with D_2O), 3.29 (s, 6H, —C(OCH$_3$)CH$_3$), 4.56 (d, 2H, —CH_2OH, collapses to a singlet with D_2O), 5.96 (s, 2H, —OCH_2O—), 6.88, 7.01 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 240 (M^+), 209 ($M^+ - CH_3O$).

Compound A**11**

6-Bromo-3,4-dimethoxyacetophenonedimethyl ketal (0.434 g, 1.42 mmol) was lithiated and treated with a solution of piperonal (0.213 g, 1.42 mmol) in dry ether at −78°C. The reaction mixture was allowed to warm up to room temperature, and worked up as in A**7** to give A**11** as an oil (0.485 g, 91%); ir (neat): 3450 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 1.52 (s, 3H, Me), 3.15 3.28, 3.76 (s, 3H each, 3MeO), 3,9 (s and overlapping m, 4H, MeO and OH), 5.94 (s, 2H, OCH_2O), 6.27 (d, 1H, C*H*OH, J = 4.49 Hz, collapses to a singlet with D_20), 6.79−6.89 (m, 4H, Ar), 7.06 (s, 1H, Ar); mass spectrum, m/z (assignment): 312 ($M^+ - 2CH_3OH$).

*Compound A***12**

Bromocyclohexane (2.04 g, 10 mmol) was added dropwise under N_2 from a syringe, while stirring, to Mg turnings (0.31 g, 12.5 mmol) in dry ether (50 mL) so that the ether refluxes gently. Stirring continued for 1 h at room temperature. A solution of 6-formylpiperonal dimethyl acetal (2.24 g, 10 mmol) in ether (50 mL) was added from a dropping funnel to the ice-cold solution. The ice bath was removed and stirring at room temperature continued for 2 hours. The resulting solution was decanted from Mg and a saturated NH_4Cl solution added. It was extracted with ether (3 × 50 mL) and the combined ether extracts washed with water (50 mL) and dried (Na_2SO_4). Removal of solvent afforded A**12** as an oil (2.98 g, 97%) which was used without further purification, ir: 3450 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 0.9−2.5 (m, 11H, C_6H_{11}) 3.3 (s, 6H, 2 MeO) 4.58 (d, 1, C*H*—OH, collapses to a singlet with D_2O), 5.5 (s, 1H, C*H*$(OMe)_2$), 5.95 (s, 2H, OCH_2O) 6.95, 7.06 (s, 1H each, Ar); mass spectrum, m/z (assignment): 277 ($M^+ - CH_3OH$), 276 ($M^+ - CH_3OH$), 245 ($M^+ - CH_3OH - CH_3O$), 244 ($M^+ - 2CH_3OH$), 193 ($M^+ - CH_3OH - C_6H_{11}$).

*Compound A***13**

2,5-Dimethoxybenzyl vinyl ether (5.0 g, 25.7 mmol) was lithiated with n-BuLi (2 equiv.) at 0°C in anhydrous pentane (150 mL, distilled over CaH_2) for 6 h, under nitrogen. The flask was placed in the freezer for 6 h to allow the solid lithio derivative to sediment. The pentane was then syringed out and dry diethyl ether (100 mL) added at 0°C. Once the anion dissolved, dry DMF (5 mL, distilled *in vacuo* from CaH_2 into NaH) was added slowly, not allowing the temperature to rise above 0°C. After 12 h at room temperature, the solution was poured in H_2O (50 mL) and washed with saturated brine solution (3 × 50 mL). The ether was dried (Na_2SO_4) and removed *in vacuo* to leave an oil. Repeated crystallizations from ether afforded 0.8 g of A**13**. Final distillation of the mother liquor (120−140°C/0.01 Torr) afforded another 0.8 g (total yield: 30%), mp 82−83°C; bp 120−124°C/0.01 Torr; ir (KBr): 1695(CHO), 1625 (C=C) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.83, 3.87 (s, 3H each, 2 × OCH_3), 4.04 (dd, 1H, J_{gem} = 2.0, J_{cis} = 6.8 Hz, vinyl H), 4.30 (dd, 1H, J_{gem} = 2.0, J_{trans} = 14.1 Hz, vinyl H), 5.12 (s, 2H, —CH_2O—), 6.55 (dd, 1H, J_{cis} 6.8, J_{trans} = 14.1 Hz,—OC*H*CH_2), 7.12 and 6.95 (ABq, 1H each, J_{ortho} = 8.2 Hz, Ar), 10.55 (s, 1H, —CHO); mass spectrum, m/z: 222 (M^+), 179 ($M^+ - OCHCH_2$): *Anal.* calcd. for $C_{12}H_{14}O_4$: C 64.86, H 6.35; found: C 64.64, H 6.09.

*Compound B***2**

The hydroxyacetal A**2** (7.0 g) was dissolved in degassed 1,2-dimethoxyethane (70 mL) and H_2O (50 mL) was added. The mixture was stirred for 24 h under N_2. The resulting white precipitate (a mixture of *cis* and *trans*, a mixture of steroisomers) was filtered and washed with diethyl ether (72%); mp 151−152°C (scaled tube); ^{1}Hmr ($CDCl_3$, 60 MHZ), δ: 5.8−6.11 (m, 5H, 2 × OCH_2O—, C(3)H), 6.35, 6.50 (s, 1H each, *cis* and *trans* C(1)H), 6.8−7.1 (m, 5H, Ar); hrms calcd. for $C_{16}H_{12}O_6$: 300.0634; found: 300.0598. *Anal.* calcd. for $C_{16}H_{12}O_6$: C 64.00, H 4.03; found: C 64.17, H 3.99.

*Compound B***5**

The hydroxyacetal A**5** (1.0 g) was placed in methanol (5 mL) and 2 *N* HCl (3 mL) added. After stirring for 8 h at room temperature, the methanol was removed *in vacuo* and the resulting oil extracted with $CHCl_3$ (3 × 10 mL). Drying (Na_2SO_4) and removal of $CHCl_3$ afforded an oil (92%) which resisted crystallization; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.38 (s, 3H, C(1)—OCH_3), 3.86, 3.87 (s, 3H each, 2 × OCH_3), 4.93 (d, 1H, J_{gem} = 12.0 Hz, C(3)H), 5.16 (dd, 1H, J_{gem} = 12.0, $J_{1,3\,trans}$ = 2.2 Hz, C(3)H), 6.13 (d, 1H, $J_{1,3\,trans}$ = 2.2 Hz, C(1)H), 6.75, 6.88 (s, 1H each, Ar); mass spectrum, m/z (assignment): 210 (M^+), 179 ($M^+ - CH_3O$); hrms calcd. for $C_{11}H_{14}O_4$: 210.0892; found: 210.0889.

*Compound B***8**

Several recrystallizations of A**8** from boiling methanol gave B**8** (88%), mp 60−61.5°C; ^{1}Hmr ($CDCl_3$, 60 MHz), δ: 3.31 (s, 3H, C(1)—OCH_3), 3.80 (s, 6H, 2 × OCH_3), 4.98 (br s, 2H, C(3)H's), 5.86 (br s, 1H, C(1)H), 6.66 and 6.82 (ABq, 1H each, J_{ortho} = 8.2 Hz, Ar): *Anal.* calcd. for $C_{11}H_{14}O_4$: C 62.84, H 6.71; found: C 62.74, H 6.80.

*Compound B***13**

Aldehyde A**13** (1.5 g) was dissolved in methanol (20 mL) and treated with $Hg(OAc)_2$ (83 mg). After 1 h, *p*-toluenesulfonic acid (21 mg) was added and 0.5 h later solid sodium bicarbonate (0.2 g) was added. The mixture was filtered and the methanol removed *in vacuo* to leave an oil. This oil was extracted into ether (2 × 10 mL), washed with H_2O (10 mL), dried (Na_2SO_4), and the ether removed to leave an oil which later crystallized from ether (90%); mp 75−76°C; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.44 (s, 3H, C(1)—OCH_3), 3.78, 3.82 (s, 3H each, 2 × OCH_3), 4.95 (d, 1H, J_{gem} = 13.1 Hz, C(3)H), 5.15 (dd, 1H, $J_{1,3\,trans}$ = 2.0, J_{gem} = 13.1 Hz, C(3)H), 6.23 (d, 1H, $J_{1,3\,trans}$ = 2.0 Hz, C(1)H), 6.75 (s, 2H, Ar); mass spectrum, m/z (assignment): 210 (M^+), 179 ($M^+ - OCH_3$). *Anal.* calcd. for $C_{11}H_{14}O_4$: C 62.85, H 6.71; found: C 62.62, H 6.43.

*Compound B***14**

Method A. Aldehyde A**13** (1.5 g) was dissolved in dioxane−water (20 mL, 7:3) and treated with $Hg(OAc)_2$ (03 g). After 3 h at room temperature, the dioxane was removed *in vacuo* and the resulting oil extracted into the $CHCl_3$ (3 × 10 mL). Drying (Na_2SO_4) and removal of $CHCl_3$ afforded a solid which was filtered and recystallized from CH_2Cl_2 (91%), mp 155−157°C (lit (9) mp 156−158°C); ir (KBr): 3450 (OH) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 2.97 (d, 1H, —OH, $J_{1,OH}$ = 7.0 Hz, disappears with D_2O), 3.80, 3.85 (s, 3H each, 2 × OCH_3), 4.97 (d, 1H, J_{gem} = 13.3 Hz, C(3)H), 5.27 (dd, 1H, $J_{1,3\,trans}$ = 2.15, J_{gem} = 13.3 Hz, C(3)H), 6.57 (dd, 1H, $J_{1,3\,trans}$ = 2.15, $J_{1,OH}$ = 7.0 Hz, collapses to a doublet in D_2O, C(1)H), 6.77 (s, 2H, Ar); mass spectrum, m/z (assignment): 196 (M^+), 179 (M^+—OH).

Method B. 4,7-Dimethoxyphthalide (1.94 g, 9.97 mmol) was dissolved in dry CH_2Cl_2 (from CaH_2, 163 mL) and cooled to −60 ± 5°C. Dibal-H (15 mL of 1.52 *M* in toluene, 22.8 mmol) was added over 0.25 h and the solution stirred a further 70 min. Methanol (5 mL) was added slowly and the mixture warmed to room temperature. The mixture was poured into $CHCl_3$ (200 mL), shaken with saturated NaCl (200 mL), and filtered through Celite. The $CHCl_3$ was dried (Na_2SO_4) and removed *in vacuo*, leaving a white solid. This was slurried in hexane and filtered, leaving 1.8 g (93%) of B**14**.

General procedure for dimethyl acetylenedicarboxylate (DMAD) adduct formation

The hydroxyacetal or phthalan (1 g) was dissolved in excess DMAD (5 mL). Glacial acetic acid (0.3 mL) was added and the mixture heated on a steam bath with swirling for 20−30 min. The excess DMAD was distilled *in vacuo* leaving a thick oil. Crystals formed upon the addition of ether were filtered, and examination of the mother liquor revealed unreacted phthalan. This could be recycled to optimize the yield.

*Compound C***1**

Adduct C**1** was prepared from A**1** by the above method in 65% yield. Crystals were obtained from ether; mp 178−180°C; ir ($CHCl_3$): 1725 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 3.75, 3.78 (s, 3H each, 2 × CO_2CH_3), 3.83, 3.84 (s, 3H each, 2 × OCH_3), 6.00 (s, 3H, —OCH_2O— and bridge H), 6.8−7.2 (m, 5H, Ar); mass spectrum, m/z (assignment): 440 (M^+), 408 ($M^+ - CH_3OH$), 298 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{23}H_{20}O_9$. C 62.71,

H 4.59; found: C 62.99, H 4.59.

Compound C2

Adduct **C2** was prepared from **A2** by the above method in 65% yield. Crystals were obtained from ether; mp 129–130°C; ir ($CHCl_3$): 1725 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz), δ: 3.68, 3.72 (s, 3H each, 2 × OCH_3), 5.93 (m, 5H, 2 × —OCH_2—O, bridge H), 6.8–7.2 (m, 5H, Ar); mass spectrum, *m/z* (assignment): 424 (M^+), 282 (5,6-methylenedioxyisobenzofuran). *Anal.* calcd. for $C_{22}H_{16}O_9$: C 62.23, H 3.81; found: C 62.31, H 3.85.

Compound C4

Adduct **C4** was prepared from **A4** by the above procedure in 65% yield, mp 159°C; ir ($CHCl_3$); 1720 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.73, 3.77 (s, 3H each, 2 × CO_2CH_3), 3.87 (s, 9H, 3 × OCH_3), 5.90 (close ABq, 2H, —OCH_2O—), 5.95 (s, 1H, bridge), 6.77 (s, 2H, Ar), 6.90 (s, 2H); hrms calcd. for $C_{24}H_{22}O_{10}$: 470.1213; found: 470.1241. *Anal.* calcd. for $C_{24}H_{22}O_{10}$: C 61.28, H 4.71; found: C 61.03, H 4.68.

Compound C5

Compound **A5** was treated as above and provided yellow crystals upon the addition of ether (95%); mp 139–139.5°C; ir ($CHCl_3$): 1710, 1730 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz), δ: 3.80 (s, 6H, 2 × CO_2CH_3), 3.80 (s, 6H, 2 × OCH_3), 5.93 (s, 2H, 2 bridge H), 7.10 (s, 2H, Ar); mass spectrum, *m/z* (assignment): 320 (M^+).

Compound C8

Adduct **A8** was treated as above and provided **C8** in 34% yield, mp 104–105°C; ir ($CHCl_3$): 1736, 1714 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 60 MHz), δ: 3.71 (s, 9H, 2 × CO_2CH_3, 1 × OCH_3), 3.98 (s, 3H, —OCH_3), 5.78 and 6.21 (ABq, 1H each, J = 1.7 Hz, 2 bridge H), 6.4 and 6.91 (ABq, 1H each, J_{ortho} = 8.7 Hz, Ar); mass spectrum, *m/z* (assignment): 320 (M^+). *Anal.* calcd. for $C_{16}H_{16}O_7$: C 60.00, H 5.04; found: C 59.97, H 5.13.

Compound C9

Adduct **C9** was prepared from **A9** in 96% yield and failed to crystalize; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 1.96 (s, 3H, CH_3), 3.76, 3.82, 3.88, 3.89 (s, 3H each, 2 × CO_2CH_3, 2 × OCH_3), 5.85 (s, 1H, bridge H), 7.0, 7.07 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 334 (M^+), 192 (5,6-dimethoxy-1-methylisobenzofuran).

Compound C10

Adduct **C10** was prepared from **A10** in 96% yield. Addition of ether afforded yellow crystals, mp 87.5–89.5°C; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 1.92 (s, 3H, CH_3), 3.76, 3.82 (s, 3H each, 2 × CO_2CH_3), 5.80 (s, 1H, bridge H), 5.95 (close ABq, 2H, J = 1.1 Hz, —OCH_2O—), 6.87, 6.93 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 3.18 (M^+), 176 (1-methyl-5,6-methylenedioxyisobenzofuran). *Anal.* calcd. for $C_{16}H_{14}O_7$: C 60.38, H 4.43; found: C 61.07, H 4.52.

Compound D6

Diels–Alder reaction of the acetal alcohol **A6** (448 mg) was done with dimethyl acetylenedicarboxylate as described in the general procedure by heating at 130°C for 20 min. Usual work-up gave the naphthol **D6** (309 mg, 62%) as a crystalline solid, mp 167°C; ir (KBr): 1735 and 1640 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.15 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.82, 3.87 (s, 3H each, $COOCH_3$), 5.85 (s, 2H, OCH_2O), 6.68 (m, 3H, Ar), 7.2, 8.2 (ABq, 2H, Ar), 12.4 (s, 1H, OH exchangeable with D_2O); mass spectrum, *m/z* (assignment): 440 (M^+), 408 ($M^+ - CH_3OH$), 393 ($M^+ - CH_3OH - CH_3$). *Anal.* calcd. for $C_{23}H_{20}O_9$: C 62.72, H 4.54; found: C 62.71, H 4.56.

Compound D7

The acetal alcohol **A7** heated wth dimethyl acetylenedicarboxylate at 130°C for 20 min with acetic acid, gave naphthol **D7** in 73% yield, mp 162°C; ip (KBr): 1720, 1645 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.33, 3.52 (s, 3H each, 2 OMe), 3.8, 3.9 (s, 6H each, 4 OMe), 3.92, 4.05 (s, 3H each, 2 – OMe), 6.55 (s, 2H, Ar), 7.68 (s, 1H, Ar), 12.35 (s, 1H, OH exchanges with D_2O); mass spectrum, *m/z* (assignment): 516 (M^+), 485 ($M^+ - CH_3OH$), 484 ($M^+ - CH_3OH$), 453 ($M^+ - CH_3OH - CH_3O$). *Anal.* calcd. for $C_{26}H_{28}O_6$: C 60.46, H 5.42; found: C 60.40, H 5.34.

Compound C11

Adduct **C11** was prepared from the ketal alcohol **A11** in 72% yield by the general procedure described above. Crystallization from ether gave yellow prisms, mp 169°C; ir (KBr): 1705, 1720 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 2.95 (s, 3H, Me), 3.69, 3.76 3.85, 3.90 (s, 3H each, 4 MeO), 6.0 (s, 2H, OCH_2O), 6.8–7.2 (m, 5H, Ar); mass spectrum, *m/z* (assignment): 454 (M^+), 408 ($M^+ - CH_3O - CH_3$). *Anal.* calcd. for $C_{24}H_{22}O_9$: C 63.43, H 4.84; found: C 63.43, H 4.84.

Compound C12

Adduct **C12** was prepared from the ketal alcohol **A12** in 70% yield. Crystallization from methanol gave light yellow prisms, mp 170°C; ir (KBr): 1700, 1725 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz) δ: 1.0–2.0 and 2.2–2.7 (m, 11H, C_6H_{11}), 3.75, 3.85 (s, 3H each, 2 MeO), 5.85 (s, 1H, bridge H), 5.92 (ABq, 2H, OCH_2O), 6.82, 6.87 (d, 2H, Ar); mass spectrum, *m/z* (assignment): 386 (M^+), 354 ($M^+ - CH_3OH$), 322 ($M^+ - 2CH_3OH$). *Anal.* calcd. for $C_{21}H_{22}O_7$: C 65.28, H 5.69; found C 65.26, H 5.70.

Compound D3

Diels–Alder reaction of **A3** with dimethylacetylenedicarboxylate in the presence of acetic acid of 100°C for 1 h gave naphthol **D3** in 62% yield, mp 167°C; ir (KBr): 1700, 1725 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz,) δ: 3.55, 3.85, 3.90, 3.92 (s, 3H each, 4 MeO), 6.05 (s, 2H, OCH_2O), 6.7–6.9 (m, 4H, Ar), 7.75 (s, 1H, Ar), 12.22 (s, 1H, OH); mass spectrum, *m/z* (assignment): 440 (M^+), 408 ($M^+ - CH_3OH$), 393 ($M^+ - CH_3OH - CH_3$). *Anal.* calcd. for $C_{23}H_{20}O_9$: C 62.72, H 4.54; found: C 62.66 H 4.60.

General procedure for the reaction of a variety of dienophiles with A5

The hydroxyacetal **A5**, glacial acetic acid, appropriate dienophile, and a suitable solvent were placed in a flask and refluxed to completion of the reaction. The flask was cooled and saturated bicarbonate added until the acetic acid was neutralized. The solvent was separated, dried (Na_2SO_4), and removed *in vacuo* to leave an oil.

Compound C5a

Acetal **A5** (0.55 g, 2.3 mmol), glacial acetic acid (0.2 mL) benzoquinone (2 equiv.), and CH_2Cl_2 (20 mL) were treated for 18 h as above. The addition of ether afforded a mixture (60%) of *endo/exo* (7:3) crystals which could not be separated. Analyses were done on the mixture; mp 10°C; ir ($CHCl_3$): 1675 (C=O), 1610 (C=C) cm^{-1}; mass spectrum, *m/z* (assignment): 286 (M^+), 278 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{16}H_{14}O_5$: C 67.12, H 4.93; found: C 67.01, H 5.09. The Hmr ($CDCl_3$, 80 MHz), endo adduct; δ: 3.65 (m, 2H, C(2), C(3)—H), 3.83 (s, 6H (2 × OCH_3) 5.68 (m, 2H, C(1), C(4)—H), 6.01 (s, 2H, —CH=CH—), 6.70 (s, 2H, Ar); exo adduct, δ: 2.80 (s, 2H, C(2), C(3)—H), 3.87 (s, 6H, 2 × OCH_3), 5.59 (s, 2H, C(1), C(4)—H) 6.80 (s, 2H, —CH=CH—), 6.90 (s, 2H, Ar).

Compound C5b

Acetal **A5** (0.5 g, 2 mmol), glacial acetic acid (0.2 mL), naphthaquinone (2.5 equiv.), and $CHCl_3$ (10 mL) were treated for 1 h as above. The excess naphthaquinone was removed on a column of silica gel using EtOAc/petrolum ether (1:1) as a solvent. The addition of ether to the resulting oil afforded the *endo* adduct but the *exo* adduct could not be isolated ^{1}Hmr showed the *endo/exo* ratio to be 3:1 and the yield was 86%. *Endo* Isomer: mp 215–217°C; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.63 (s, 6H, 2 × OCH_3), 3.8 (m, 2H, C(2), C(3)—H), 5.81 (m, 2H, C(1), C(4)—H), 6.63 (s, 2H, Ar), 7.47–7.85 (AA'BB' pattern, 4H, Ar); mass spectrum, *m/z* (assignment): 336 (M^+), 178 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{20}H_{16}O_5$: C 71,42, H 4.79; found: C 71.67, H 4.84.

Compound C5c

Acetal **A5** (4.3 g, 17.7 mmol), glacial acetic acid (1.9 mL), methyl vinyl ketone (3 equiv. freshly distilled, and 1% hydroquinone added as an inhibitor), and CCl_4 (100 mL) were heated t 60°C for 6 h. The addition of ether afforded *endo* crystals. The oil from the mother liquor was run through a gravity of column of silica gel using benzene/acetone (4:1). The faster spot (R_f = 0.52) afforded *endo*

crystals and the slower spot (R_f = 0.50) *exo* crystals upon the addition of ether. The yield was 78% and the *endo/exo* ratio was 3:2. *Endo* Adduct: mp 129–131°C; ir ($CHCl_3$): 1710 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 1.83 (dd, 1H, $J_{\alpha,3\beta}$ = 11.7, $J_{2,3\alpha}$ = 4.1 Hz, C(3α)—H), 1.99 (s, 3H, $COCH_3$), 2.22 (ddd, 1H, $J_{3\alpha,3\beta}$ = 11.7, $J_{2,3\beta}$ = 9.5, $J_{3\beta,4}$ = 4.6 Hz, C(3β)—H), 3.40 (ddd, 1H, $J_{1,2}$ = 5.1, $J_{2,3\alpha}$ = 4.1, $J_{2,3\beta}$ = 9.5 Hz, C(2)—H), 3.83, 3.86 (s, 3H each, 2 × OCH_3), 5.38 (d, 1H, $J_{3\beta,4}$ = 4.6 Hz, C(4)—H), 5.53 (d, 1H, $J_{1,2}$ = 5.1 Hz, C(1)—H), 6.79, 6.87 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 248 (M^+), 178 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{14}H_{16}O_4$: C 67.73, H 6.50; found: C 67.54, H 6.87. *Exo* Adduct: mp 88–90°C; ir ($CHCl_3$): 1710 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$ 80 MHz), δ: 1.66 (dd, 1H, $J_{3\alpha,3\beta}$ = 11.5, $J_{2,3\alpha}$ = 8.8 Hz, C(3α)—H), 2.88 (s, 3H, $COCH_3$), 2.29 (ddd, 1H, $J_{3\alpha,3\beta}$ = 11.5, $J_{3\beta,4}$ = 4.6, $J_{2,3\beta}$ = 4.4 Hz, C(3β)—H), 2.59 (dd, 1H, $J_{2,3\alpha}$ = 8.8, $J_{2,3\beta}$ = 4.4 Hz, (C(2)—H), 3.87 (s, 6H, 2 × OCH_3), 5.43 (d, 1H, $J_{3\beta,4}$ = 4.6 Hz, C(4)—H), 5.50 (s, 1H, C(1)—H), 6.89 (s, 2H, Ar); mass spectrum, *m/z* (assignment): 248 (M^+), 178(5,6-dimethoxyisobenzofuran): *Anal.* calcd. for $C_{14}H_{16}O_6$: C 67.73, H 6.50; found C 67.76, H 6.62.

Compound C5e

Acetal A5 (0.5 g, 2 mmol), glacial acetic acid (0.5 mL), acrylonitrile (6 equiv., freshly distilled, and 1% hydroquinone added as an inhibitor), and $CHCl_3$ (5 mL) were treated as above for 4 h. The addition of ether to the oil afforded *endo* crystals (64%). The ^{1}Hmr showed an *endo/exo* ratio 9:1 and the *exo* adduct could not be isolated. *Endo* Adduct: mp 184–187°C; ir ($CHCl_3$): 2200 (CN) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 1.61 (dd, 1H, $J_{3\alpha,3\beta}$ = 11.6, $J_{2,3\alpha}$ = 4.03 Hz, C(3α)—H), 2.52 (ddd, 1H, $J_{3\alpha,3\beta}$ = 11.6, $J_{2,3\beta}$ = 10.6, $J_{3\beta,4}$ = 4.15 Hz, C(3β)—H), 3.19 (ddd, 1H, $J_{1,2}$ = 4.15, $J_{2,3\alpha}$ = 4.03, $J_{2,3\beta}$ = 10.6 Hz, C(2)—H), 3.88 (s, 6H, 2 × OCH_3), 4.57 (t, 2H, $J_{1,2}$ = $J_{3\beta,4}$ = 4.15, C(1) and C(4)—H), 6.91, 7.05 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 231 (M^+), 178 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{13}H_{13}NO_3$: C 67.52, H 5.67, N 6.06; found: C 67.35, H 5.72, N 6.12.

Compound C5f

Acetal A5 (0.5 g, 2.0 mmol), glacial acetic acid (0.2 mL), α-chloroacrylonitrile (0.5 mL), and CH_2Cl_2 (10 mL) were treated as above for 18 h. The oil was run through a silica gel column, but failed to crystallize upon the addition of ether (70%). There was a major and minor isomer (7:3) but the stereochemistry could not be determined; ir ($CHCl_3$): 1205 (C—O) cm^{-1}; mass spectrum, *m/z* (assignment): 265 (M^+), 178 (5,6-dimethoxyisobenzofuran). The ^{1}Hmr ($CDCl_3$, 80 MHz), minor isomer, δ: 2.39 (d, 1H, $J_{3\alpha,3\beta}$ = 12.9 Hz, C(3β)—H), 2.75 (dd, 1H, $J_{3\alpha,3\beta}$ = 12.9, $J_{3\alpha,4}$ = 4.4 Hz, C(3α)—H), 3.91, 3.94, (s, 3H each 2 × OCH_3), 5.4–5.6 (m, 2H, C(1), C(4)—H), 7.13, 7.40 (s, 1H each, Ar); major isomer, δ: 1.84 (d, 1H, $J_{3\alpha,3\beta}$ = 12.7 Hz, C(3β)—H), 3.10 (dd, 1H, $J_{3\alpha,3\beta}$ = 12.7, $J_{3\alpha,4}$ = 4.9 Hz, C(3α)—H), 3.87 (s, 6H, 2 × OCH_3), 5.4–5.6 (m, 2H, C(1) and C(4)—H), 6.90, 7.05 (s, 1H each Ar).

Compound C5h

Acetal A5 (0.5 g, 2.0 mmol), glacial acetic acid (0.5 mL), methyl acrylate (3 equiv., freshly distilled, and 1% hydroquinone added as an inhibitor), and $CHCl_3$ (10 mL) were treated as above for 10 h. Addition of ether afforded the *endo* isomer. Attempts to isolate the *exo* isomer were unsuccessful. The *endo/exo* ratio was 3:2 and the yield was 50%. *Endo* Adduct: mp 105–107°C; ir ($CHCl_3$): 1740 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 1.74 (dd, 1H, $J_{3\alpha,3\beta}$ = 11.6, $J_{2,3\alpha}$ = 3.8 Hz, C(3α)—H), 2.31 (ddd, 1H, $J_{3\alpha,3\beta}$ = 11.6, $J_{3\beta,4}$ = 5.16, $J_{2,3\beta}$ = 10.3 Hz, C(3β)—H), 3.4 (ddd, 1H, $J_{1,2}$ = 5.16, $J_{2,3\alpha}$ = 3.8, $J_{2,3\beta}$ = 10.3 Hz, C(2)—H), 3.52 (s, 3H, —CO_2CH_3), 3.82, 3.85 (s, 3H each, 2 × OCH_3), 5.39 (d, 1H, $J_{3\beta,4}$ = 5.16 Hz, C(4)—H), 5.50 (d, 1H, $J_{1,2}$ = 5.16 Hz, C(1)—H), 6.8, 6.85 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 264 (M^+), 178 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{14}H_{16}O_5$: 63.63, H 6.10; found: C 63.24, H 6.32.

Compound C5i

Acetal A5 (1.02 g), glacial acetic acid (0.41 mL), acrolein (1.14 mL), and $CHCl_3$ (10 mL) were treated as above for 30 h. The addition of ether afforded *endo* crystals. The oil from the mother liquor was placed on a silica gel column. The faster spot (R_f = 0.55) gave *endo* crystals and the slower spot (R_f = 0.52) *exo* crystas upon the addition of ether (63%; *endo/exo* ratio 3:2). *endo* Adduct:: mp 103–104°C; ir (KBr): 1720 C=O), 2720 (CHO) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), see Table 3. High resolution ms calcd. for $C_{13}H_{14}O_4$: 234.0892; found: 234.0884. *exo* Adduct: mp 73–74°C; ir (KBr):1715 (C=O), 2710 (CHO) cm^{-1}; ^{1}Hmr ($CDCl_3$, 400 MHz), see Table 3. High resolution ms calcd. for $C_{13}H_{14}O_4$: 234.0892; found: 234.0903.

Compound C5d

Into a refluxing solution of 2-butenolide (0.4 g, 4.75 mmol) and $CHCl_3$ (10 mL) was added a mixture of acetal A5 (0.46 g, 1.9 mmol), glacial acetic acid (0.2 mL), and $CHCl_3$ (10 mL). After 48 h at reflux, the resolution was cooled and saturated bicarbonate added until the acetic acid was neutralized. The $CHCl_3$ was separated, dried (Na_2SO_4), and removed *in vacuo* to leave an oil. The excess butenolide was removed *via* a high vacuum distillation. The remaining oil was passed through a silica gel column. The faster spot (R_f = 0.6) gave *exo* crystals and the slower (R_f = 0.53) *endo* crystals upon the addition of ether/CH_2Cl_2. The yield was 72% and the *endo/exo* ratio was 1:2 *exo* Aduct. mp 177–178°C; ir ($CHCl_3$): 1765 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 2.6–3.0 (m, 2H, C(2) and C(3)—H), 3.85 (s, 6H, 2 × OCH_3), 4.2–4.8 (m, 2H, —CH_2O—), 5.29 (s, 1H, C(4)—H), 5.65 (s, 1H, C(1)—H), 6.87, 6.92 (s, 1H each, Ar); mass spectrum, *m/z* (assignment): 262 (M^+), 178 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{14}H_{14}O_5$: C 64.12, H 5.38; found C 63.91, H 5.33. *endo* Adduct: mp 184–185°C; ir ($CHCl_3$): 1765 (C=O) cm^{-1}; ^{1}Hmr ($CDCl_3$, 80 MHz), δ: 3.4–4.3 (m, 4H, C(2,3) and —CH_2O—), 3.85, 3.87 (s, 3H each, 2 × OCH_3), 5.4 (d, 1H, $J_{3,4}$ = 5.1 Hz, C(4)—H), 5.59 (d, 1H, $J_{1,2}$ = 5.02 Hz, C(1)—H), 6.93 (s, 2H, Ar); mass spectrum, *m/z* (assignment): 262 (M^+), 178 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{14}H_{14}O_5$: C 64.12, H 5.38; found: C 63.80, H 5.28.

Compound C5g

To a mixture of acetal A5 (0.5 g, 2.0 mmol) and glacial acetic acid (0.2 mL) was added acetic anhydride (0.1 mL) and maleic anhydride (0.6 g, 6.1 mmol) in CH_2Cl_2 (5 mL). The mixture was refluxed 24 h, cooled, and saturated bicarbonate added until neutral. The CH_2Cl_2 was dried (Na_2SO_4) and removed *in vacuo* to leave an oil. The addition of ether resulted in a mixture of *endo/exo* (7:3) crystals (60%) which could not be separated. Analyses were done on the mixture: mp 214–217°C; ir (KBr): 1760–1850 (C=O) cm^{-1}; mass spectrum, *m/z* (assignment): 276 (M^+), 178 (5,6-dimethoxyisobenzofuran). *Anal.* calcd. for $C_{14}H_{12}O_6$: C 60.87, H 4.38; found: C 60.53, H 4.52. The ^{1}Hmr ($CDCl_3$, 80 MHz), *endo* isomer; δ: 3.87 (s, 6H, 2 × OCH_3), 4.00 (m, 2H, C(2) and C(3)—H), 5.70 (m, 2H, C(1) and C(4)—H), 6.90 (s, 2H, Ar); *exo* isomer; δ: 3.20 (s, 2H, C(2) and C(3)—H), 3.87 (s, 6H, 2 × OCH_3), 5.85 (s, 2H, C(1) and C(4)—H), 6.96 (s, 2H, Ar).

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