Anomalous 5-*endo-trig* reversals: general reactions of 7-oxabicyclo[2.2.1]heptenes and heptanes

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Two general 5-*endo-trig* reversals of 7-oxabicyclo[2.2.1]heptanes and heptenes are described and discussed. The reverse-Michael reaction occurs with the aldehyde, ketone, ester, and nitrile derivatives while the reverse aldol reaction catalysed by acid is confined to the aldehydes and ketones. These properties of the title compounds are rationalized in terms of the geometric alignments of the bonding and antibonding orbitals of the bridging oxygen atom and its neighboring carbons. New isobenzofuran and cyclohexadiene syntheses form a part of the report.

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On décrit et on discute de deux réactions générales 5-*endo-trig* inversées des oxa-7 bicyclo[2.2.1] heptanes et heptènes. La réaction inverse de Michael se produit dans le cas des dérivés de l'aldéhyde, de la cétone et du nitrile tandis que la réaction aldolique inverse se limite aux aldéhydes et aux cétones. On rationalise ces propriétés des composés mentionnés dans le titre en fonction des alignements des orbitales liantes et antiliantes de l'atome d'oxygène en position de pont et de ses atomes de carbone voisins. On rapporte également de nouvelles synthèses de l'isobenzofuranne et du cyclohexadiène.

[Traduit par le journal]

Early in our studies of the Diels–Alder reactions of isobenzofurans (1) we made the useful and intriguing discovery that adduct **1***a* was smoothly converted to the dihydronaphthalene **2***a* with methanolic sodium methoxide. The same reaction applied to the closely related adduct **3** was a key transformation in our recent synthesis (2) of (±) daunomycinone. An examination of the process with a variety of oxabicyclo adducts[2] was conducted and the results (Table 1, Entries 1, 3, 6, 8, 11, 13, 16, 18) confirmed the generality of the reaction. A reverse-Michael rationalization shown in Scheme 1 requires the development of some double bond character at a bridgehead and is also a 5-*endo-trig* reversal in violation of rules (3) formulated earlier and illustrated (4) with the furan **9**. No evidence could be obtained, however, to support any alternative mechanism; for example, no products of C(4)—O cleavage were ever observed, thus excluding the possibility of a simple nucleophilic displacement at C(1) and(or) C(4). Deuteration at C(2) took place with esters and nitriles (entries 5, 7, 10, 12, 15, and 17) and the deuterated products were *endo–exo* mixtures even when pure *endo* substrates (**1***c* and **1***d*, entries 5 and 7) were used. Oxabicyclo ketones and aldehydes could not be deuterated cleanly with methanolic methoxide because of the rapid formation of products under the conditions. After 1 h at 20°C with this reagent, **1***a* and **1***b*, for example, were converted to a 1:1 mixture of products (**2***a* and **2***b* respectively) and deuterated starting materials. The lower acidity of the esters and nitriles must be responsible for rapid reprotonation of their enolates in methanolic methoxide, permitting clean deuteration in these cases and revealing the existence of a kinetic barrier to the reverse-Michael fission of the C(1)—O bond. This behaviour is similar to the previously observed (4) deuteration of furan **9** and is interpreted similarly. Unlike the simple furan **9**, however, which was inert to all bases, these compounds do suffer a forbidden 5-*endo-trig* cleavage with the strong base LDA under aprotic conditions (entries 6, 8, 11, 13, 16, and 18). Base-catalysed aromatizations observed in entries 2, 4, and 9 and previously with sodium acetate in refluxing methanol (5) must also occur through an initial reverse-Michael cleavage followed by dehydration. Thus it is clear that the 7-oxabicyclo heptanes and heptenes are susceptible to a general 5-*endo-trig* reversal[3] in violation of Baldwin's rules and that this anomaly cannot be attributed to thermodynamic factors, i.e. release of strain resulting from the reaction.

Again, in the course of our studies on the synthesis of (±) daunomycinone, we obtained the surprising result that the hydrogenolysis of **3** in ethanol containing a few drops of perchloric acid produced not the expected tetralin but the phthalan **10** (95%). In attempting to understand the course of this unusual hydrogenolytic cleavage of the C(1)—C(2) bond, we subjected ketone **1***a* to perchloric acid – methanol treatment at room temperature for 5 min and obtained methoxy phthalan **11** (94%) whose structure was supported by spectroscopic data and by conversion to the Diels–Alder adduct **12** (72%) with dimethyl acetylene dicarboxylate. In the absence of methanol, similar acid treatment resulted in extensive decomposition, probably through the formation of isobenzofuran **13** which polymerizes. No aromatic product (**8***a*) could be detected. Evidently these ketones are extremely prone to reverse-aldol cleavage (Scheme 2) and the resulting oxonium ion is trapped as the alkoxy phthalan which may be isolated (**11**) or hydrogenolysed (**10**). In the absence of an alcohol, the hydroxy phthalan that might be formed instead is easily dehydrated to an unstable isobenzofuran **13**. We have previously observed that hydroxy phthalans (hemi-acetals) are much more unstable to acid than methoxy phthalans (acetals). In accordance with this rationale, we found that the stable isobenzofuran **14** provided a methyl vinyl ketone adduct **15**[4] that in turn produced a stable isobenzofuran **16** (95%) upon treatment with sulfuric acid, and the furanoid adduct **4***a* yielded furan **17** (78%) and acetophenone (13%). Aldehyde **1***b* behaved similarly but the re-

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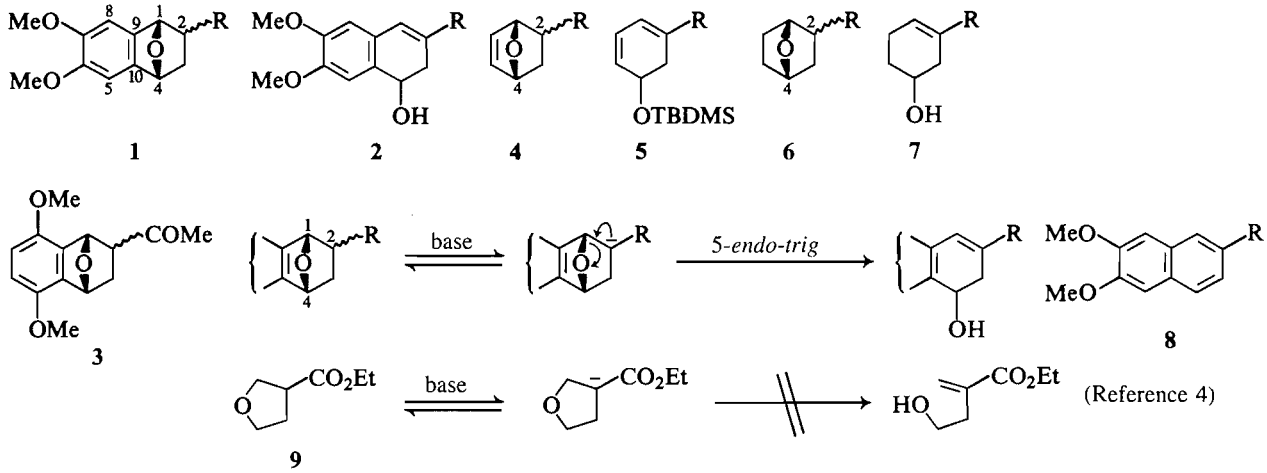
[2] Prepared by Diels–Alder reaction of furans and isobenzofurans with the appropriate dienophiles and used as *endo–exo* mixtures.

[3] Some of our results have been recently confirmed; see ref. 6.

[4] Compound **14** was prepared in this laboratory (D. Rajapaksa and R. Rodrigo, unpublished work). Both **14** and **16** were characterized by mass, ^{1}H nmr and ir spectroscopy but could not be obtained pure enough for elemental analysis.



a (R = COMe) *b* (R = CHO) *c* (R = CO_2Me) *d* (R = CN)

SCHEME 1. Reverse-Michael reactions

TABLE 1. Reverse-Michael reactions

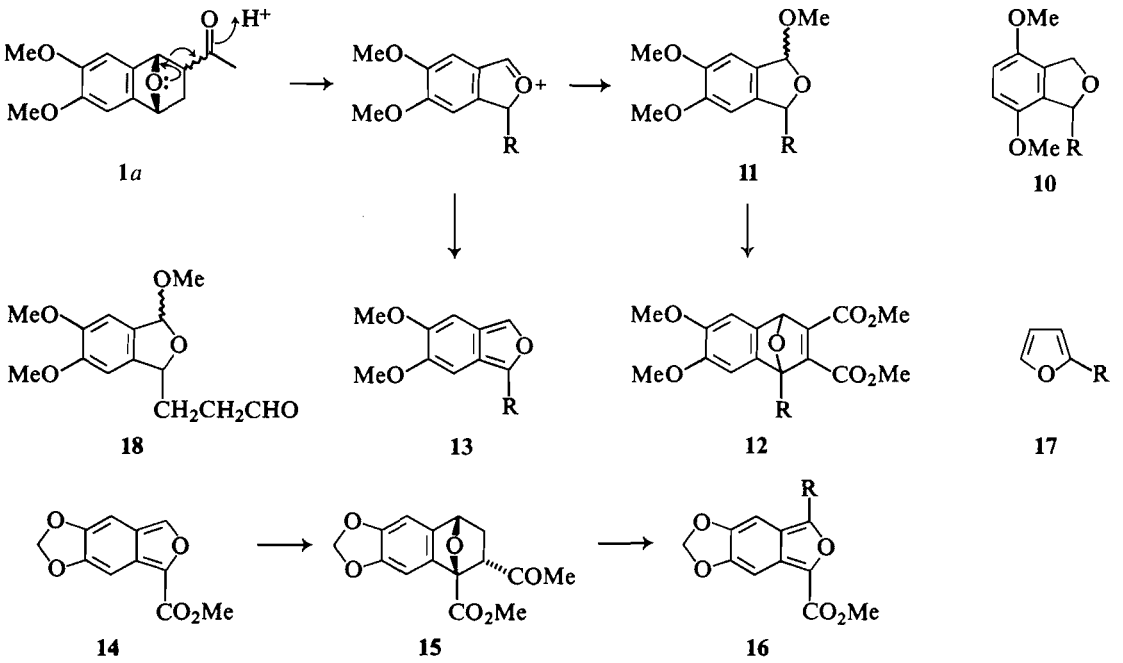
Entry	Bridged substrate*	Conditions: Base, solvent, temp (°C)	Product (isolated yield, %)
1.	**1***a*	NaOMe, MeOH, 20	**2***a* (90)
2.	**1***a*	NaOME, MeOH, 65	**8***a* (90)
3.	**1***b*	NaOMe, MeOH, 20	**2***b* (83)
4.	**1***b*	NaOMe, MeOH, 65	**8***b* (92)
5.	**1***c* (*endo* isomer)	NaOMe, MeOD, 20	2-Deuterio-**1***c* (95)*
6.	**1***c*	LDA, THF, 0	**2***c* (72)
7.	**1***d* (*endo* isomer)	NaOMe, MeOD, 65	2-Deuterio-**1***d* (95)*
8.	**1***d*	LDA, THF, −78	**2***d* (79)
9.	**4***a*	NaOMe, MeOH, 20	Acetophenone (90)
10.	**4***c*	NaOMe, MeOD, 20	2-Deuterio-**4***c* (95)*
11.	**4***c*	LDA, THF, 0	**5***c* (65)†
12.	**4***d*	NaOMe, MeOD, 65	2-Deuterio-**4***d* (95)*
13.	**4***d*	LDA, THF, −78	**5***d* (60)†
14.	**6***a*	NaOMe, MeOH, 20	**7***a* (60)
15.	**6***c*	NaOMe, MeOD, 20	2-Deuterio-**6***c* (95)*
16.	**6***c*	LDA, THF, 0	**7***c* (50)
17.	**6***d*	NaOMe, MeOD, 65	2-Deuterio-**6***d* (95)*
18.	**6***d*	LDA, THF, −78	**7***d* (65)

* *exo*–*endo* Mixtures unless otherwise specified.
† Isolated as TBDMS derivative after silylation.

sults were less clear-cut because of the formation and persistence of its dimethyl acetal (80%) under the same conditions. The existence of phthalan **18** (5%) and its dimethyl acetal (15%) was evident in the nmr spectrum of the reaction mixture. Ester and nitriles **1***c*, **1***d*, **4***c*, and **4***d* were indefinitely stable to the same conditions; **1***c* and **1***d* provided napthalenes **8***c* and **8***d* (50 and 69% respectively) after refluxing for 8 h, but **4***c* and **4***d* underwent extensive decomposition and no aromatic product was detected. Furan adducts are known to undergo reverse Diels–Alder reactions at moderate temperatures (7) and this might be responsible for the latter result. Similar ring disruptions of Diels–Alder adducts of both furan (8) and isobenzofuran (9) have been reported. The general reverse-aldol process described above is also a 5-*endo-trig* reversal in violation of Baldwin's rules. Like the reverse-Michael fission previously described, its occurrence cannot merely be a manifestation of strain release because it is difficult to see how **1***a* and **15**, for instance, can be converted into virtually non-aromatic isobenzofurans instead of aromatizing to stable naphthalenes, or how **1***b* can be content with forming an acetal instead of undergoing acid-catalysed aromatization to **8***b* (or the acetal thereof).

Other 5-*endo-trig* cyclizations have been reported (10) and those involving additions to immonium (11) and oxonium (12) double bonds rationalized on the basis of increased flexibility and decreased vectorial specificity, both consequences of the greater single bond character of these double bonds. Such explanations are clearly inapplicable to our reverse-Michael reactions, nor can any increase in carbonium ion character of the oxonium ion intermediate (Scheme 2) of our retro-aldol reactions provide enough flexibility for the reaction to occur in either direction.

X-ray crystallographic analyses (13) of the isobenzofuranoid adducts **1***a* and **1***c* established that the furanoid moiety (C(1)—C(2)—C(3)—C(4)—O) in each compound is rigidly held in two planes (C(1)—O—C(4) and C(1)—C(2)—



SCHEME 2. Retro-aldol reactions (R = $CH_2CH_2COCH_3$)

C(3)—C(4)) at 121.6° to each other. This geometry, quite unlike the simple furan **9**, is responsible in our opinion for the prevalence of the anomalous 5-*endo-trig* reversals. Enolate ions, formed in the reverse-Michael reaction, have a large coefficient (14) at C(2) in their HOMO and this orbital at C(2) is properly aligned in these systems (but not in the furan **9**) to interact with the relatively low-lying antibonding orbital of the C(1)—O bond (LUMO), weakening this bond and allowing the C(1)—C(2) π-bond to develop as the reaction proceeds (Fig. 1). Such a frontier orbital interaction decreases the kinetic barrier to the reverse-Michael reaction in the oxabicyclo systems. In the norbornyl radical of similar geometry, the well-known *exo*-specificity displayed in its reactions has been attributed (15) to interaction between the C—C bridge orbital and singly occupied *p* orbital at C(2).

The same molecular architecture accounts for the reverse-aldol process. One of the orbitals containing a non-bonded pair of electrons on the bridge oxygen atom is aligned antiperiplanar to the C(1)—C(2) bond. Interaction of this orbital (HOMO) with the antibonding orbital of the C(1)—C(2) bond (LUMO) results in weakening of the C(1)—C(2) bond and the growth of some π-bonding between C(1) and the oxygen (Fig. 2). Similar interactions in axial α-halogenotetrahydropyrans result in bond lengthening (C—X) and shortening (O—C) and have also been invoked to interpret the anomeric effect as a stabilizing influence (16). The presence of a protonated substituent at C(2) (aldehyde or ketone as in **1***a*, **4***a*, and **1***b*) provides a low energy pathway (retro-aldol) for bond breaking (C(1)—C(2)) and bond making (C(1)—O, π-bond) to take place, resulting in the formation of the cyclic oxonium ion. Esters and nitriles (**1***c*, **1***d*, **4***c*, and **4***d*) with their lower basicity are not known to undergo the acid-catalysed retro-aldol reaction and are therefore inert under the conditions. The behaviour of **4***a*, which prefers to form a furan **17** rather than aromatize to acetophenone by a 6:1 margin (78% **17**, 13% acetophenone) when exposed to acid, can thus be understood.

The synthetic potential of the reactions described herein must not be overlooked. We have used the reverse-Michael reaction for short stereocontrolled syntheses (17) of some shikimic acids, and other applications to natural product synthesis are underway. The reverse-aldol reactions represent an unprecedented isobenzofuran → 1-substituted isobenzofuran conversion, which adds an extra element of versatility to our general isobenzofuran synthesis (1).

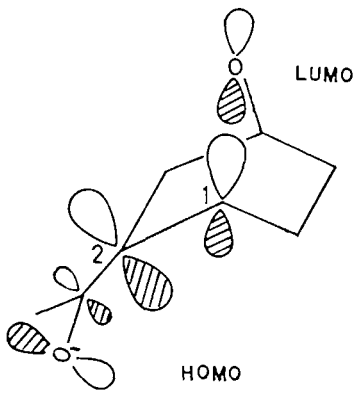


FIG. 1

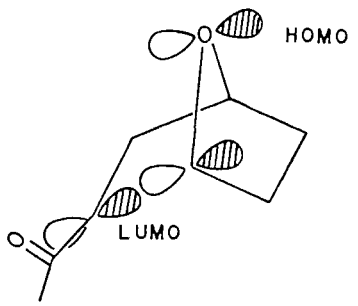


FIG. 2

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 Bruker WP-80 or Bruker WH-400 spectrophotometers. Samples were run in $CDCl_3$ solutions containing tetramethylsilane as an internal standard and chemical shifts (δ) and coupling constants (Hz) measured directly. 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. Combustion analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario and(or) Canadian Microanalytical Service Ltd., Vancouver, British Columbia.

General procedure for deuteration of **1**c, **1**d, **4**c, **4**d, **6**c, *and* **6**d

The bicyclo adduct dissolved in methanol-d_1 was treated with sodium methoxide (3 equiv. freshly prepared from sodium and methanol-d_1) and the mixture stirred at the appropriate temperature (Table 1) for 2 h. D_2O was added and carbon dioxide bubbled through until the solution was neutral to pH paper. The methanol was removed under reduced pressure, the residue extracted into chloroform, and the solvent removed. The residual material was distilled or crystallized.

3-Acetyl-1,2-dihydro-1-hydroxy-6,7-dimethoxynaphthalene **2**a

The bicyclo ketone **1***a* (1 g), dissolved in methanol (15 mL), was treated with sodium methoxide (3 equiv. freshly prepared from sodium and methanol) and the mixture stirred at room temperature for 2 h. Water was added and carbon dioxide bubbled through until the solution was neutral to pH paper. The methanol was removed under reduced pressure, the residual material extracted with chloroform, and the extracts washed with water. Removal of the solvent and crystallization from dichloromethane gave **2***a* (90%), mp 158–162°C; ir ($CHCl_3$): 3400, 1650 cm^{-1}; ^1H nmr: 2.05 (d, 1H, $J_{1,OH}$ = 5.7 Hz; disappears with D_2O, —OH), 2.44 (s, 3H, —COMe), 2.6–3.2 (m, 2H, C(2)—*H*), 3.92, 3.95 (s, 3H each, 2 × OMe), 4.85 (dt, 1H, $J_{1,OH}$ = 5.7, $J_{1,2\alpha} = J_{1,2\beta}$ = 6.1 Hz, collapses to a triplet with D_2O, C(1)—H), 6.86, 7.04 (s, 1H each, 2 × Ar), 7.42 (broad s, 1H, vinyl-H); mass spectrum (intensity, assignment): 248 (8, M^+), 230 (76, $M^{\cdot+} - H_2O$), 215 (100, $M^{\cdot+} - H_2O - CH_3$). *Anal.* calcd. for $C_{14}H_{16}O_4$: C 67.73, H 6.50; found: C 67.38, H 6.47.

3-Formyl-1,2-dihydro-1-hydroxy-6,7-dimethoxynaphthalene **2**b

The bicyclo aldehyde **1***b* (1.5 g) was treated with sodium methoxide as described. Recrystallization from dichloromethane afforded **2***b* (83%), mp 132–134°C; ir ($CHCl_3$): 3400 (OH), 1660 (C=O) cm^{-1}; ^1H nmr: 2.4–2.9 (m, 3H, C(2)—H's and —OH), 3.9, 3.94 (s, 3H each, 2 × OMe), 4.86 (t, 1H, $J_{1,2}$ = 4.2 Hz, C(1)—H), 6.88, 7.06 (s, 1H each, 2 × Ar), 7.29 (broad s, 1H, vinyl-H), 9.61 (s, 1H, —CHO); mass spectrum (intensity, assignment): 234 (12, $M^{\cdot+}$), 216 (100, $M^{\cdot+} - H_2O$). *Anal.* calcd. for $C_{13}H_{14}O_4$: C 66.66, H 6.02; found: C 66.32, H 6.10.

2-Acetyl-6,7-dimethoxy naphthalene **8**a

The ketone **1***a* (1 g) was treated in the same manner as described for the preparation of **2***a* and the solution refluxed for 4 h. After neutralization and work-up as before, the residue was crystallized from methylene chloride (90%), mp 109–110°C; ir ($CHCl_3$): 1680 cm^{-1}; ^1H nmr: 2.69 (s, 3H), 4.03 (s, 6H), 7.15, 7.23 (s, 2 × 1H, H(5), H(8)), 7.71 (d, 1H, J = 8.5 Hz, H(4)), 7.92 (dd, 1H, J = 8.5 and 1.7 Hz, H(3)), 8.33 (d, 1H, J = 1.7 Hz, H(1)); mass spectrum: 230 ($M^{\cdot+}$), 215 ($M^{\cdot+}$ —CH_3). *Anal.* calcd. for $C_{14}H_{14}O_3$: C 73.03, H 6.13; found: C 73.25, H 6.20.

2-Formyl-6,7-dimethoxynaphthalene **8**b

The aldehyde **1***b* was treated as above and the product **8***b* crystallized from ether (92%), mp 86.5–88°C; ir ($CHCl_3$): 1695 (C=O) cm^{-1}; ^1H nmr: 4.04 (s, 6H), 7.18–7.26 (m, 2H), 7.8–8.19 (m, 3H), 10.10 (s, 1H, CHO); mass spectrum: 216 ($M^{\cdot+}$), 215 ($M^{\cdot+} - H$). *Anal.* calcd. for $C_{13}H_{12}O_3$: C 72.21, H 5.59; found: C 72.51, H 5.69.

3-Carbomethoxy-1,2-dihydro-1-hydroxy-6,7-dimethoxy naphthalene **2**c

Freshly prepared lithium diisopropylamide (1.1 equiv. in dry THF) was added to a solution of the ester **1***c* (0.1 g, 0.38 mmol) in dry THF (5 mL) at 0°C under nitrogen. Water (3 mL) was added after 10 min and the mixture poured into $CHCl_3$ (10 mL). After extraction with $CHCl_3$ (2 × 10 mL) the extracts were dried and the solvent removed to leave a solid which crystallized from ether (72%), mp 148–149°C; ir (KBr): 3450 (OH), 1720 (C=O) cm^{-1}; ^1H nmr: 1.81 (d, 1H, disappears with D_2O, —OH), 2.61–3.15 (m, 2H, C(2)—H's), 3.81, 3.89, 3.93 (s, 3H each, 2 × Ar—*OMe*, 1 × CO_2Me), 4.80 (q, 1H, collapses to a triplet with D_2O, J = 5.7 Hz, C(1)—H), 6.82, 7.01 (s, 1H each, Ar), 7.56 (broad s, 1H, vinyl-H); mass spectrum (intensity, assignment); 264 (18, $M^{\cdot+}$), 246 (100, $M^{\cdot+} - H_2O$). *Anal.* calcd. for $C_{14}H_{16}O_5$: C 63.63, H 6.10; found: C 63.36, H 6.04.

3-Cyano-1,2-dihydro-1-hydroxy-6,7-dimethoxy naphthalene **2**d

The cyanide **1***d* was treated with LDA as above at −78°C and the product **2***d* isolated and crystallized from dichloromethane (79%), mp 147–148°C; ir (KBr): 3480 (OH), 2200 (CN) cm^{-1}; ^1H nmr: 1.81 (d, 1H, disappears with D_2O, —OH), 2.73 (dd, 2H, J = 1.6 and 5.3 Hz, C(2)—H's), 3.90, 3.94 (s, 3H each, 2 × OMe), 4.82 (q, 1H, collapses to a triplet with D_2O, J = 5.3 Hz, C(1)—H), 6.75, 6.93 (s, 1H each, 2 × Ar), 7.19 (t, 1H, J = 1.6 Hz, vinyl-H); mass spectrum (intensity, assignment): 231 (1.5, $M^{\cdot+}$) 213 (100, $M^{\cdot+} - H_2O$). *Anal.* calcd. for $C_{13}H_{13}NO_3$: C 67.52, H 5.67, N 6.06; found: C 67.19, H 5.64, N 5.97.

*Acetophenone from 2-acetyl-7-oxabicyclo[2.2.1]hept-5-ene (***4**a)

Ketone **4***a* (0.25 g) in absolute methanol (3 mL) under nitrogen was treated with sodium methoxide as before and stirred at room temperature for 24 h. After work-up as before acetophenone (90%) was isolated and identified.

*1-*tert*-Butyldimethylsilyloxy-3-carbomethoxy-1,2-dihydrobenzene* **5**c

Freshly prepared LDA (1.2 equiv.) was added to a stirred solution of the ester **4***c* (4 g) in dry THF (25 mL) at 0°C under nitrogen. After 10 min, saturated aqueous ammonium chloride (10 mL) was added, THF removed, and the residue extracted into dichloromethane. The extract was dried (Na_2SO_4) and the solvent removed. The residue was treated with triethylamine (1.2 equiv.), dimethylamino pyridine (1 g), *tert*-butyldimethylsilylchloride (1.1 equiv.), and methylene chloride (100 mL) and stirred at room temperature for 12 h. The reaction mixture was filtered through a short column of silica gel using ethyl acetate – hexane (1 : 1) as the eluant. The solvents were removed and the residue distilled to provide **5***c* (65%), bp 86°C/0.05 Torr; ir (neat): 1712 (C=O); ^1H nmr: 0.04 (s, 6H, 2 × Me), 0.85 (s, 9H, *t*-Bu), 2.61 (dd, 1H, J = 9.0 and 1.7 Hz, —CH_2—), 3.73 (s, 3H, —CO_2Me), 4.48 (dt, 1H, J = 1.7 and 9.0 Hz, C*H*OR), 6.03 (m, 2H, vinyl-H's), 6.96 (m, 1H, vinyl-H); mass spectrum (intensity, assignment): 268 (4, $M^{\cdot+}$), 266 (7, $M^{\cdot+}$ − *t*-Bu). *Anal.* calcd. for $C_{14}H_{24}SiO_3$: C 62.64, H 9.01; found: C 62.55, H 8.89.

*1-*tert*-Butyldimethylsilyloxy-3-cyano-1,2-dihydrobenzene* **5**d

Freshly prepared LDA (1.2 equiv.) was added to a stirred solution of the cyanide **4***d* (3.68 g) in dry THF (25 mL) under nitrogen at −78°C. The reaction was processed as above and the product **5***d* (60%) obtained after distillation, bp 80°C/0.02 Torr; ir (neat): 2200 (CN) cm^{-1}; ^1H nmr: 0.07 (s, 6H, 2 × Me), 0.87 (s, 9H, *t*-Bu), 2.54 (dd, 2H, J = 1.7 and 8.0 Hz, —CH_2—), 4.40 (dt, 1H, J = 1.2 and 8.0 Hz, C*H*OR), 6.05 (m, 2H, vinyl-H's), 6.70 (m, 1H, vinyl-H); mass spectrum (intensity, assignment): 235 (3, $M^{\cdot+}$), 178 (100, $M^{\cdot+}$ − *t*-But). *Anal.* calcd. for $C_{13}H_{21}NOSi$: C 66.33, H 8.99, N 5.95; found: C 66.32, H 8.91, N 5.93.

1-Acetyl-5-hydroxy-cyclohexene **7**a

The ketone **6***a* (1 g) dissolved in dry methanol (5 mL) under nitrogen was treated with sodium methoxide and the reaction worked up as previously; ir (neat): 3400 (OH), 1655 (C=O); ^1H nmr: 1.5–2.8 (m, 6H, 3 × —CH_2—), 2.29 (s, 3H, —COMe), 3.10 (broad s, 1H, disappears with D_2O, —OH), 3.8–4.2 (m, 1H, —C*H*OH), 6.8–7.0

(m, 1H, vinyl-H); mass spectrum (intensity, assignment): 140 (45, $M^{+\cdot}$), 97 (100, $M^{+\cdot} - C_2H_3O$). *Anal.* calcd. for $C_8H_{12}O_2$: C 61.52, H 7.74; found: C 61.12, H 7.82.

1-Carbomethoxy-5-hydroxy-cyclohexene 7c

The ester **6***c* (1 g) in dry THF (30 mL) under nitrogen, was treated with LDA (1.1 equiv.) at 0°C. The reaction was processed as before to provide the oily product **7***c* which was distilled (50%) bulb-to-bulb; ir (neat): 3400 (OH), 1655 (C=O) cm^{-1}; ^1H nmr: 1.5–2.8 (m, 6H, 3 × —CH_2—), 2.29 (s, 3H, —COMe), 3.10 (broad s, 1H, disappears with D_2O, —OH), 3.8–4.2 (m, 1H, —C*H*OH), 6.8–7.0 (m, 1H, vinyl-H); mass spectrum (intensity, assignment): 140 (45, $M^{+\cdot}$), 97 (100, $M^{+\cdot} - C_2H_3O$). *Anal.* calcd. for $C_8H_{12}O_2$: C 61.52, H 7.74; found: C 61.12, H 7.82.

1-Cyano-5-hydroxy-cyclohexene 7d

The cyanide **6***d* (1 g) in dry THF (30 mL) under nitrogen was treated with LDA (1.1 equiv.) at −78°C. The reaction was processed as before to provide the oily product **7***d* which was distilled (65%) bulk-to-bulb; ir (neat): 3400 (OH), 2208 (CN) cm^{-1}; ^1H nmr: 1.5–2.8 (m, 6H, 3 × —CH_2—), 3.8–4.2 (m, 1H, C*H*OH), 6.55–6.8 (m, 1H, vinyl-H); mass spectrum (intensity, assignment): 123 (1, $M^{+\cdot}$), 105 (100, $M^{+\cdot} - H_2O$), 80 (100 $M^{+\cdot} - C_2H_3O$). *Anal.* calcd. for C_7H_9NO: C 68.27, H 7.37, N 11.37; found: C 68.30, H 7.48, N 11.11.

1,3-Dihydro-4,7-dimethoxy-1-(3-oxobutyl)isobenzofuran ***10***

Ketone **4** (400 mg) was placed in ethanol (50 mL) containing 10% Pd/C (80 mg) and perchloric acid (25 drops). The mixture was hydrogenated at 40 psi for 8 h and filtered through Celite. Saturated bicarbonate was added (30 mL) and the ethanol removed *in vacuo*. The residue was extracted into chloroform (20 mL), dried, and the solvent removed to yield an oil (95%) which resisted crystallization; ir (neat): 1730 (C=O) cm^{-1}; ^1H nmr: 2.05 (s, 3H, COC*H*$_3$), 2.0–2.6 (m, 4H, CH_2—CH_2), 3.7 (s, 6H, 2 × OMe), 4.97 (m, 2H, CH_2—O), 5.3 (m, 1H, CH—O), 6.6 (s, 2H, ArH); ^{13}C nmr: 29.0 (t, *C*H$_2$—CH_2COMe), 29.95 (q, CO*C*H$_3$), 39.62 (t, —CH_2*C*H$_2$COMe), 55.79 (q, 2 × Ar—OMe), 71.7 (t, *C*H$_2$—O), 83.4 (d, *CH*—O), 110.3, 110.4 (d each, aromatic *C*—H), 129.4, 130.6 (s each, aromatic *C*—OMe), 208.9 (s, C=O); mass spectrum: 250 (8, $M^{+\cdot}$), 192 (91, $M^{+\cdot}$ − CH_3COCH_3), 179 (100, $M^{+\cdot} - CH_2CH_2COCH_3$).

1,3-Dihydro-1,5,6-trimethoxy-3-(3-oxobutyl)isobenzofuran ***11***

The ketone **1***a* (50 mg) in methanol (2 mL) was treated with perchloric acid (3 drops) at room temperature. The solution was neutralized with aqueous sodium bicarbonate after 5 min and extracted into ether (2 × 10 mL). The extracts were dried (Na_2SO_4) and the ether removed to leave an oil which was filtered through a column of silica gel with ethyl acetate − ligroin (1 : 1). The oil did not crystallize and ^1H nmr showed it to be a 1 : 1 mixture of diastereomers (94% total yield); ir (neat): 1705 (C=O) cm^{-1}; ^1H nmr (a 1 : 1 mixture of *cis* and *trans* diastereomers): 1.5–2.8 (m, 7H of each isomer, 2 × —CH_2— and COMe), 3.40, 3.50 (s, 3H each, phthalan-OMe of each isomer), 3.91 (s, 6H, 2 × ArOMe of each isomer), 5.0–5.5 (m, 1H of each isomer, C(3)—H), 6.01 (s, 1H, C(1)—H of *cis* isomer), 6.11 (d, 1H, C(1)—H of *trans* isomer), 6.71, 6.88 (s, 1H each of each isomer, Ar); mass spectrum (intensity, assignment): 280 (5, $M^{+\cdot}$), 248 (48, $M^{+\cdot}$ − MeOH), 222 (100, McLafferty rearrangement).

2,3-Dicarbomethoxy-1,4-epoxy-1,4-dihydro-6,7-dimethoxy-1-(3-oxobutyl)naphthalene ***12***

The dihydroisobenzofuran **11** (240 mg) dissolved in dimethyl acetylene dicarboxylate (1.5 mL) and glacial acetic acid (0.1 mL) was heated on a steam bath for 1 h. The liquids were removed under high vacuum and residual thick oil crystallized from ether (72%), mp 83–84°C; ir (KBr): 1700 (C=O), 1720 (C=O); ^1H nmr: 2.16 (s, 3H, COMe), 2.68 (broad s, 4H, 2 × —CH_2), 3.77, 33.80 (s, 3H each, 2 × CO_2Me), 3.87 (s, 6H, 2 × ArOMe), 5.85 (s, 1H, bridge-H), 6.95, 7.04 (s, 1H each, Ar); mass spectrum (intensity, assignment): 390 (56, $M^{+\cdot}$), 248 (100, isobenzofuran). *Anal.* calcd. for $C_{20}H_{22}O_8$: C 61.53, H 5.68; found: C 61.39, H 5.72.

1-Carbomethoxy-3-(3-oxobutyl)-5,6-methylenedioxy isobenzofuran ***16***

The adduct **15**[4] (100 mg) was heated under reflux in CH_2Cl_2 (20 mL) with concentrated H_2SO_4 (2 drops in 1 mL of MeOH) for 15 min. The reaction mixture was allowed to cool and washed with an aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted again with CH_2Cl_2 (10 mL). The combined extracts were dried (Na_2SO_4) and the solvent removed. Addition of ether (5 mL) formed an amorphous powder, which was filtered off (95 mg, 95%); ir (KBr): 1690 (C=O), 1740 (C=O) cm^{-1}; ^1H nmr: 2.13 (s, 3H, $COCH_3$) 2.8–3.3 (m, A_2B_2 system —CH_2CH_2—) 3.9 (s, 3H, COOMe), 5.93 (s, 2H, OCH_2O), 6.65, 7.70 (s, 1H each, 2Ar); mass spectrum (intensity, assignment): 290 (67, $M^{+\cdot}$), 259 (22, $M^{+\cdot}$ − OMe) 247 ($M^{+\cdot}$ − COMe).

1-(3-Oxobutyl)furan ***17***

Ketone **4***a* (1 g) was dissolved in methanol (2 mL) and treated with perchloric acid (2 drops) at room temperature. The mixture was stirred for 24 h, and saturated bicarbonate added to neutralize the acid. Removal of the methanol, followed by extraction into methylene chloride (2 × 25 mL), drying, and removal of the solvent afforded a 6 : 1 mixture of **17** and acetophenone. The mixture was separated on a silica gel column using ethyl acetate – ligroin (1 : 1) as solvent, yielding acetophenone (13%) and the furan **17** (ref. 18) (78%); ir (neat): 1710 (C=O) cm^{-1}; ^1H nmr: 2.21 (s, 3H, COMe), 2.7–3.0 (m, 4H, 2 CH_2's), 6.0, 6.35, 7.32 (broad s, 1H each, 3 furan H's); mass spectrum (intensity, assignment): 138 (3, $M^{+\cdot}$), 123 (100, $M^{+\cdot}$ − CH_3).

2-Carbomethoxy-6,7-dimethoxy naphthalene 8c

Ester **1***c* (0.5 g) was placed in methanol (5 mL), perchloric acid (3 drops) added, and the mixture refluxed for 8 h. It was cooled, neutralized with saturated sodium bicarbonate, the methanol removed, and the residue extracted with chloroform (2 × 10 mL). The extracts were dried and the solvent removed to leave a solid crystallized from chloroform to provide **8***c* (50%), mp 103–105°C; ^1H nmr: 3.95 (s, 3H, CO_2*Me*), 4.00 (s, 6H, 2 × OMe), 7.13, 7.2 (s, 1H each, Ar—H), 7.68 (d, 1H, J_{ortho} = 8.5 Hz, C(4)—H), 7.93 (dd, 1H, J_{ortho} = 8.5 Hz, J_{meta} = 1.4 Hz, C(3)—H), 8.44 (broad s, 1H, C(1)—H); mass spectrum: 246 (100, $M^{+\cdot}$), 215 (53, $M^{+\cdot}$ − OMe). *Anal.* calcd. for $C_{14}H_{14}O_4$: C 68.28, H 5.73; found: C 68.01, H 5.80.

2-Cyano-6,7-dimethoxy naphthalene 8d

Cyanide **1***d* (0.2 g) was treated in the same was as **1***c* and the product isolated similarly (69%), mp 116–118°C; ir (KBr): 2210 cm^{-1}; ^1H nmr: 4.05 (s, 6H, 2 × OMe), 7.15 (s, 2H, C(5)—H and C(8)—H), 7.47 (dd, 1H, J_{ortho} = 8.3 Hz, J_{meta} = 3.8 Hz, C(3)—H), 7.74 (d, 1H, J_{ortho} = 8.3 Hz, C(4)—H), 8.07 (broad s, 1H, C(1)—H); mass spectrum: 213 (100, $M^{+\cdot}$). *Anal.* calcd. for $C_{13}H_{11}NO_2$: C 73.22, H 5.20, N 6.57; found: C 73.34, H 5.12, N 6.38.

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