Relevance of Conformational Constraints to the Regioselective Lithiation of Aromatic Diethers. Application to the Convenient Construction of the DEF Tricyclic Subunit of the Austalides

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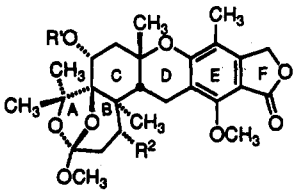
The lithiation of **29** and **30** is shown to occur at all three sites with a dissimilar kinetic preference. For the dihydrofuran, reaction at the proton labeled $H_{\beta'}$ operates predominantly; in the dihydropyran example, H_α is the favored site of deprotonation. These protons represent those that are the most deshielded in the respective ^1H NMR spectra. The same is true for **9** and **19**, both of which undergo metalation adjacent to the ring oxygen. No crossover in regioselectivity is observed, presumably because the methoxy substituent is sterically precluded from rotating freely. Mixed complexes (dimers, etc.) or mixed aggregates in low equilibrium concentration are key to understanding the acidification phenomenon of ortho hydrogens. As a consequence of the dominance of regiocontrol by the ring oxygen in **9**, a convenient means has been developed for elaboration of the tricyclic eastern sector of the austalide mycotoxins.

Among the toxigenic agents produced by *Aspergillus ustus*, the meroterpenoid metabolites known as austalide A–E (**1–5**) hold a particularly prominent position.[2] Although additional austalides, e.g., **6**, have become known

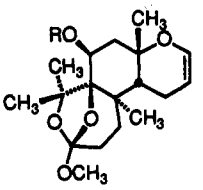


1, A: R' = Ac R^2 = H
2, B: R' = H R^2 = H
3, C: R' = Ac R^2 = OAc
4, D: R' = H R^2 = OAc
5, E: R' = Ac R^2 = OH
6, F: R' = H R^2 = OH

more recently[3] and biogenetic links to mycophenolic acid have been established,[4] the distinctive heterocyclic array present in these structurally complex orthoesters has only very recently yielded to synthesis.[5]

The polycyclic structural features of the austalide mycotoxins are not known elsewhere in nature. Four of the six serially-fused rings contain oxygen atoms in quite different chemical environments. As a consequence, austalide A (**1**) and its analogs are attractive synthetic targets.

Since the tetracyclic ABCD subunit **7** has already been assembled in this laboratory,[6] our attention has logically been turned to a disconnection involving the pyran/*p*-cresol/butenolide triad **8**. Should it be possible to assemble



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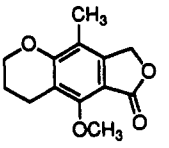

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8 in ready fashion from dihydropyran,[7] the possible adoption of this process to **7** could ultimately serve as one means for assembling **1** and its congeners by *de novo* synthesis.

From the retrosynthetic vantage point, the construction of benzylic alcohol **9** was considered desirable *provided that* the introduction of a methyl group at site α and of a carboxyl group at site β could be accomplished in a respectably regioselective manner (Scheme 1). Our established goal was to achieve this objective by directed ortho lithiation,[8] despite the fact that little, if any, information existed concerning the relative capacities of identical heteroatoms in different structural settings to control substitution patterns. As we shall show, alkoxy and cyclic ethers can indeed exhibit disparate capabilities in such kinetically-controlled reactions, but only when previously unrecognized structural features become incorporated.[9] Also to be discussed is a stereocontrolled means for arriving at **10** from **11**. The latter building block is available by condensation of 6-lithiodihydropyran[10] with dimethylformamide. The conversion of **10** into **9** was expected to be accomplished in expedient fashion.

Results

Although oxygen substituents of various type have previously been found to be capable of directing the ortho

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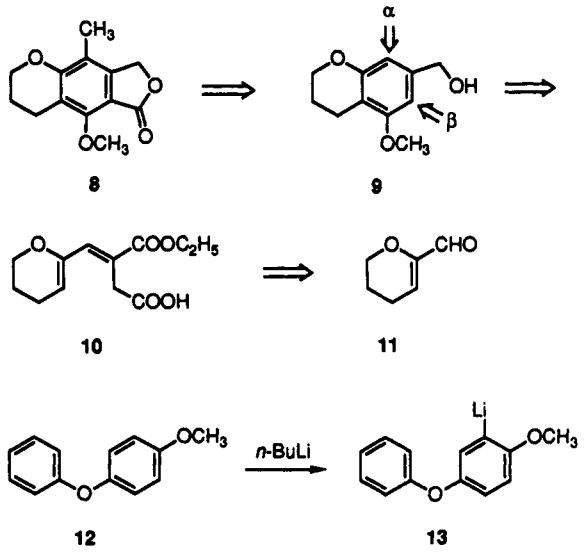
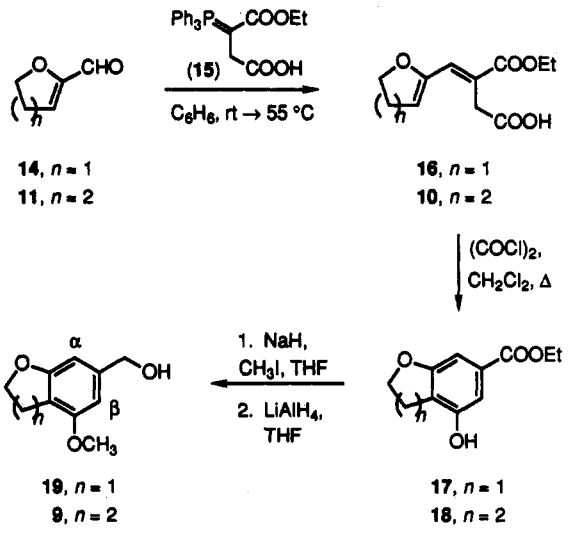
Scheme 1



Scheme 2



metalation of aromatic rings,[8,11,12] experiments in which they have been allowed to vie competitively for an alkyllithium reagent are rare. In the only example that has come to our attention, the diphenyl ether **12** was purported to undergo lithium/hydrogen exchange adjacent to the methoxyl group exclusively. This claim appears in two reviews,[13,14] but the original paper cited in these works does not address this actual process.[15]

In order to allow for the possibility that ether oxygens in differently sized rings might exhibit modulated directing capacities related to enforced geometric variations and the like, attention has been accorded collectively to fused 5- and 6-membered heterocyclic pairs.

The Meta Dioxygenation Plan. The conversion of 2,3-dihydrofuran to **14** had been described by Russian workers.[16] A modification of their procedure was developed to improve efficiency. Chain extension of both **11** and **14** was undertaken with the multifunctional Wittig reagent **15**, which Hudson and Chopard showed is readily available from maleic anhydride, triphenylphosphine, and ethanol.[17] We were attracted to the use of this ylide on the strength of a report published by Röder and Krauss[18] where it was established that 3-alkylidenesuccinic acid monomethyl esters are produced in highly stereoselective fashion upon condensation with aldehydes. The vinylic hydrogen atom in the products invariably eventuates cis to the carbethoxy substituent. Under the present circumstances, the *E*-isomers **16** and **10** were likewise produced exclusively, as revealed by NOE studies at 300 MHz (Scheme 2). Since **14** is a particularly sensitive substance, its reaction with **15** was necessarily conducted at or below 40 °C. The more robust nature of **11** allowed for greater variation in reaction conditions. Yields of **10** maximized at 89% when the reactants were heated to 55 °C in benzene for 1.5 days.

As a direct consequence of their *E*-stereochemistry, both **16** and **10** underwent spontaneous cyclization to the bicyclic phenols **17** and **18**, respectively, when warmed with oxalyl chloride in CH_2Cl_2 solution. This annulation is mediated by intramolecular nucleophilic attack on the intermediate acyl chloride by the neighboring enol ether. O-methylation and lithium aluminum hydride reduction completed the route to **19** and **9**.

The structural relationship of these products to benzyl alcohol and its 3,5-dimethoxy derivative is quite apparent. Both parent molecules are recognized to be capable of ring metalation.[19,20] Their inherent symmetry does not, however, allow for an analysis of directive effects. In 3-methoxybenzyl alcohol, deprotonation occurs predominantly at C-2 as expected.[20,21] The two doubly activated sites in **9** and **19**, labeled as α and β for convenience, are nonequivalent and at least superficially give the appearance of being so closely balanced electronically that lithium/hydrogen exchange should be rather indiscriminate. In actuality, however, the alkoxy and cyclic ether oxygen atoms exhibit distinctively different capabilities for directing ortho lithiation.

Two sets of conditions were adopted for exposure of **9** and **19** to *n*-butyllithium. One set of reactions was conducted in benzene at 20 °C for 60 min (A). The second series of experiments, labeled as B in Table 1, was performed in ether containing 2 equiv of TMEDA. The three electrophiles DMF, solid carbon dioxide, and benzaldehyde were introduced 1 h later. In all examples, metalation at the site immediately adjacent to the cyclic ether oxygen was found to be kinetically favored. The most striking result is the exclusivety of α attack (within experimentally detectable limits) exhibited by **9** in benzene solution to give **20b–22b**. This exceptional selectivity persisted in additional experiments involving a more bulky base such as *tert*-butyllithium and sterically more de-

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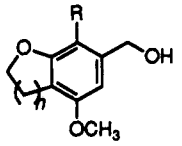
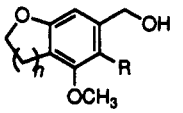
Table 1. Lithiation Reactions Involving 9 and 19

compd	reaction condns[a]	electrophile	product yield, %	α/β ratio
19	A	DMF	69	77:23
	B	DMF	62	78:22
9	A	DMF	69	>97:<3
	B	DMF	65	68:32
19	A	$CO_{2(s)}$	48[b]	79:21
	B	$CO_{2(s)}$	72[b]	81:19
9	A	$CO_{2(s)}$	59[b]	>97:<3
	B	$CO_{2(s)}$	56[b]	72:28
19	A	PhCHO	54	82:18
	B	PhCHO	50	83:17
9	A	PhCHO	60	>97:<3
	B	PhCHO	49	70:30

[a] See text. [b] Based on recovered starting material.



20, R = CHO
21, R = COOH (as lactone)
22, R = CH(OH)Ph
a, $n = 1$; **b**, $n = 2$



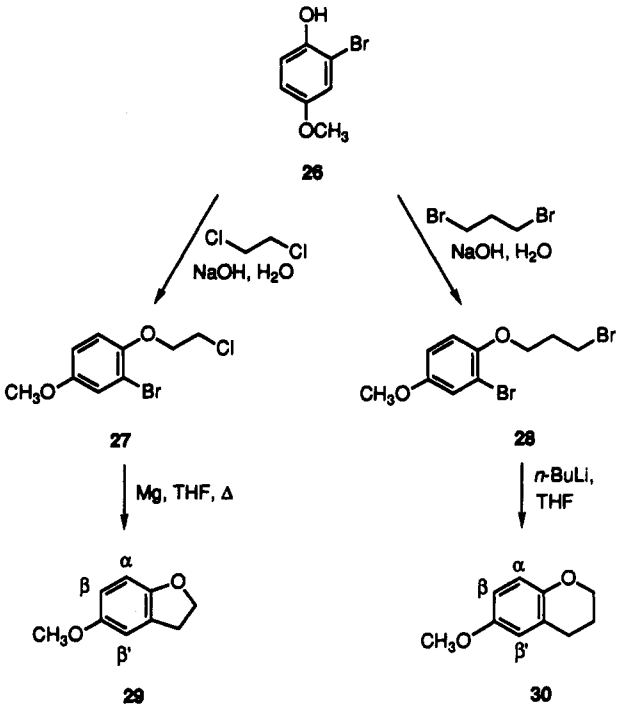
23, R = CHO
24, R = COOH (as lactone)
25, R = CH(OH)Ph
a, $n = 1$; **b**, $n = 2$

manding electrophiles such as *N*-formylpiperidine and *N*-methylformanilide. The response of **19** was entirely analogous. With both substrates, some leveling of the α/β ratio was noted when a solvent and additive capable of coordination to lithium was present. On no occasion, however, were **23–25** formed as the dominant product. The structural assignments to **20–22** were confirmed by NOE measurements. In all six examples, double irradiation of the methoxyl singlet induced integral enhancement of the aryl proton signal. This was not the case for **23–25**.

Para Orientation of the Oxygenated Centers. Since steric factors resident in the ground states of **9** and **19** will be shown to play an important role in their response to directed metalation, cross-over comparison with similarly functionalized aromatic diethers lacking nonbonded constraints was mandatory. In 5-methoxy-2,3-dihydrobenzofuran (**29**) and -pyran (**30**), the methoxyl substituent possesses total freedom of rotation and lacks any predetermined conformational bias. Consequently, these starting materials were accessed from a common precursor as depicted in Scheme 3. Bromination of *p*-methoxyphenol in CS_2 solution[22] furnished **26**. Introduction of the requisite haloalkyl chains was achieved by generation of the phenoxide ion under phase-transfer conditions with the appropriate dihalide present in large excess.[23] While **27** underwent ready cyclization under Grignard conditions to produce **29** (73%), the conversion of **28** to **30** was best achieved (86%) under Parham conditions[24] involving the use of *n*-butyllithium.

To enable direct comparison, recourse was made to the same two reaction conditions and two of the three previous electrophiles. Monomeric formaldehyde[25] was substituted for benzaldehyde to allow for structural interconversions between products as detailed below. The designation of reaction sites continues to be α for the aryl proton adjacent

Scheme 3



26
27
28
29
30

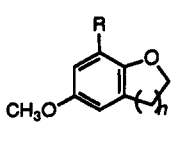
Table 2. Lithiation Reactions Involving 29 and 30

compd	reaction condns[a]	electrophile	product yield,[b] %	$\alpha/\beta/\beta'$ ratio
29	A	*N*-formylpiperidine	54	9:21:70
	B	*N*-formylpiperidine	79	11:26:63
30	A	*N*-formylpiperidine	72	55:19:23
	B	*N*-formylpiperidine	57	45:22:33
29	A	$CO_{2(s)}$; CH_2N_2	36	20:8:72[c]
	B	$CO_{2(s)}$; CH_2N_2	38	24:12:64
30	A	$CO_{2(s)}$; CH_2N_2		49:18:33
	B	$CO_{2(s)}$; CH_2N_2		40:18:42[c]
29	A	CH_2O	50	31:21:48
	B	CH_2O	51	28:14:58
30	A	CH_2O	50	55:21:24
	B	CH_2O	73	53:24:22

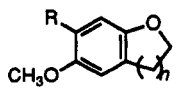
[a] See text. [b] Based on recovered starting material. [c] Single experiment.

to the cyclic ether oxygen. In **29** and **30**, there are now two C–H bonds positioned ortho to the methoxyl substituent. These options are differentiated by the symbols β and β' as indicated on the structural formulas. As before, the reactions were performed minimally in duplicate except where noted.

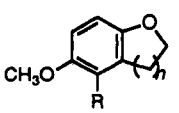
Aldehydes **31**, **34**, and **37** were cleanly separated in both series by gravity column chromatography and individually identified on the strength of the splitting patterns in the aromatic region of their 300-MHz ^1H NMR spectra.[26]



31, R = CHO
32, R = $COOCH_3$
33, R = CH_2OH
a, $n = 1$; **b**, $n = 2$



34, R = CHO
35, R = $COOCH_3$
36, R = CH_2OH
a, $n = 1$; **b**, $n = 2$



37, R = CHO
38, R = $COOCH_3$
39, R = CH_2OH
a, $n = 1$; **b**, $n = 2$

Neither the ester nor the alcohol mixtures were amenable to chromatographic separation. The major isomer in each instance could be obtained pure by preparative gas

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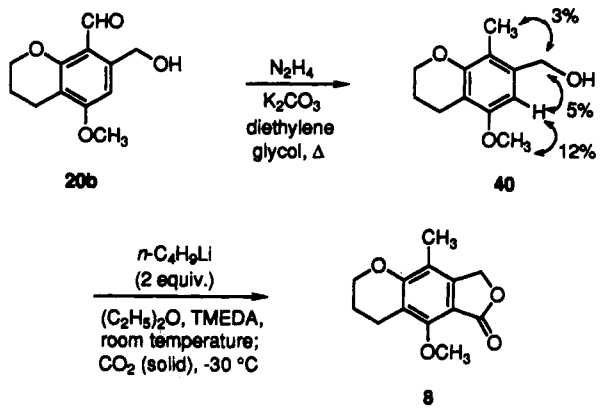
Scheme 4



chromatography. In these experiments, suitable integration of expanded ^{1}H NMR spectra was utilized to determine product composition. Pure samples of furanyl and pyranyl alcohols **33**, **36**, and **39** were generated by hydride reduction of the corresponding aldehydes. Independent reduction of esters **38a** and **38b** to **39a** and **39b**, respectively, provided further corroboration of the structural assignments.

The available experimental facts indicate that the β' proton of **29** experiences deprotonation most readily in all situations. In the case of **30**, metalation at the α position occurs with the greatest facility. The extent of lithiation decreases in the order $\alpha > \beta' > \beta$. A comparable progression was not seen for **29**, although metalation at its α position was second most favorable in those reactions involving CO_2 and formaldehyde. That this was not seen during condensation with *N*-formylpiperidine reflects to some degree the error limits associated with product isolation when very polar compounds are formed as in the carboxylation and hydroxymethylation reactions.

Construction of the Eastern Sector of the Austalides. With acquisition of quantities of **20b** in isomerically pure condition, its conversion into **8**, the entire eastern sector of the austalide mycotoxins, was undertaken.[7] By application of the Wolff–Kishner reduction, **20b** was transformed into the colorless, crystalline methyl-substituted benzylic alcohol **40** in 60% yield (Scheme 4). Further confirmation that the requisite positional isomer had been obtained was derived from NOE studies. Particularly relevant was the observation that the remaining aryl proton was positioned in close spatial proximity to *both* the $-OCH_3$ and $-CH_2OH$ substituents. Lactone **8** was then secured by lithiation of **40** with *n*-butyllithium in ether containing TMEDA and ensuing carboxylation. Lactonization occurred spontaneously upon workup to deliver **8** in 60% yield.

In this way, a direct route to **8** has been opened up that takes advantage of two regiocontrolled aryl metalation steps. Many other applications of this technology can be envisioned, and it is anticipated that these will be adapted in the years ahead.

Discussion

The long-held mechanistic perception of directed ortho lithiation, when reduced to its simplest terms, is the operation of three distinct steps defined as follows: (a) coordination of the heteroatom to one or more aggregates of the alkyllithium reagent; (b) deprotonation of a neighboring aryl-bound proton; and (c) ultimate capture of the electrophile.[8] The extent of activation is inextricably linked to the nature of the substituent, and priority ordering has been available since 1976.[27] The various relative rankings, e.g., $CONR_2 > SO_2NR_2 > CH_2NH_2 > OMe > NR_2 > CF_3 > F$, reveal ether oxygens to exhibit only modest capability. Nevertheless, complex formation between lithiating reagents and aryl ethers has been directly observed in several NMR studies.[11b,28] Recently, Schleyer and his co-workers have questioned whether complex formation between the lithiating reagent and the aromatic substrate is truly essential.[28d] They argue that should "strong complexation [be held] responsible for the high regioselectivity, the reactions should proceed more slowly since the complexation energy would have to be overcome in going to the transition state. However, if the energy of the transition state is lowered more than that of the initial complex, the reactions will be accelerated, as is observed experimentally." They prefer to view the role of electronegative substituents as a transition state phenomenon stemming from an electronically favorable charge arrangement and strong Li–O coordination such that the actual metalation is kinetically enhanced.

Slocum has identified 10 factors that influence the ability of a substituent to direct ortho lithiation.[29] Of these, direct electronic π-interaction (or the lack thereof) has been uncovered to be the major control element. As the result of more recent studies by this research team, "this feature coupled with the perceived coordinating ability of the directing group [and] its electron-withdrawing capability through the σ-framework [are considered to] provide sufficient criteria to predict the efficiency of a directing group to effect metalation."[30]

Thus, although little kinetic and thermodynamic information is available for directed ortho lithiations, it has been ascertained that protophilic attack is rate-determining (k_H/k_D = 6–8)[31] and that equilibration between lithiated intermediates is slow at low temperatures.[32] Since the rates of deprotonation are inductively controlled, resonance interactions involving the nonbonded lone pairs on oxygen gain considerable importance. When delocalization operates to the maximum extent, the capacity for O–Li coordination is significantly reduced. Concomitantly, the acidity of the ortho protons decreases because of charge buildup on their associated carbon atoms. As a consequence of this analysis, any decrease in the ability of an ether oxygen to engage in resonance via either of its

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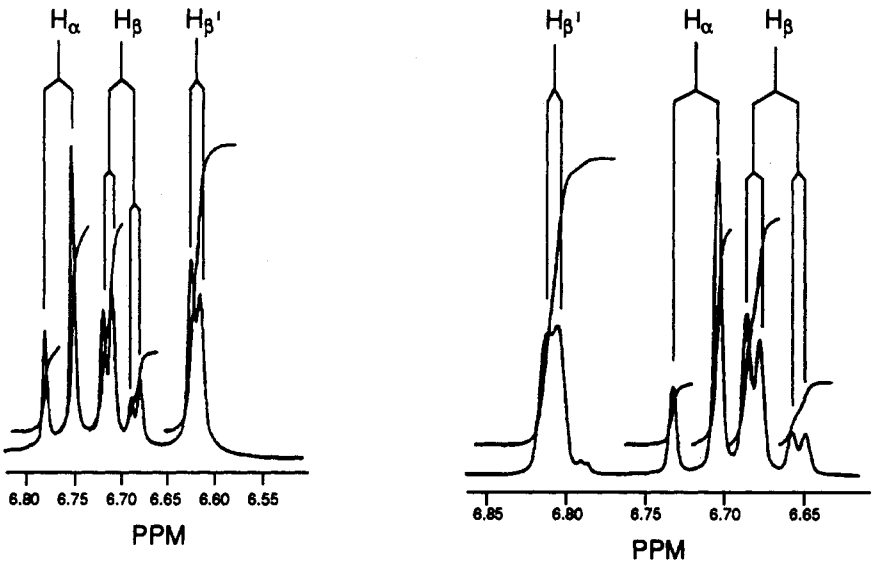
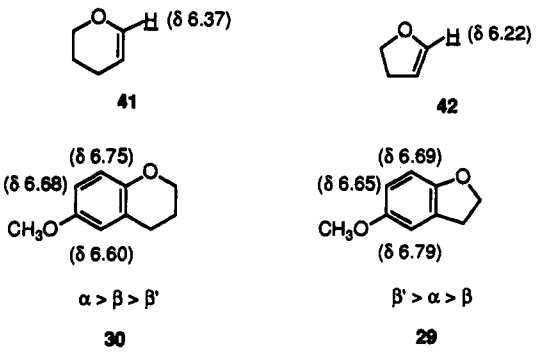


Figure 1. Expanded scale downfield regions of the 300-MHz ^{1}H NMR spectra of **30** (left) and **29** (right) showing the different relative chemical shift orderings of the three aryl protons.

electron pairs should be expected to result in enhanced regioselectivity. To our knowledge, no serious consideration appears to have been accorded to steric control of ortho metalation reactions. As will be seen below, structural arrangements such as those present in **9** and **19** are capable of overriding operation of labilizing effects originating from resonance contributions.

The limited effort addressed at elucidation of the mechanistic details of the metalation step has provided indication both experimentally[11b,28d] and theoretically[33] that the reactive reagent is the *n*-butyllithium dimer present in low equilibrium concentration. An agostic Li---H_{ortho} interaction has been invoked in addition to heteroatom coordination as a means by which regioselectivity arises.[34] In our view, the involvement of mixed complexes or mixed aggregates in low equilibrium concentration is key to our understanding of the acidification phenomenon not only of ortho hydrogens, but also of meta[35] and peri hydrogens[36] as well as more remote sites.[37] Thus, if complexation is taken for granted, the central issue becomes preorganization of the substrate in that manner necessary for attaining the transition state. In this context, the benzopyran system is better able to preorganize for lithiation (smaller ΔG^*) than the benzodihydrofuran analog because of the different O–C–C angle and directionality of electron pairs on oxygen.

Given that the relative kinetic reactivity for ortho lithiations is linked to a significant degree to the inductive contribution of the heteroatom substituent, a relationship between the preferred reaction site and ^{1}H NMR chemical shift should be recognizable. Indeed, a close parallel should exist between oxygenated aromatics and vinyl ethers. The latter class of compounds has been intensively scrutinized. It is widely recognized that attachment of an alkoxy substituent to an unconjugated double bond results in acidification of the α-proton[10] as a direct consequence of inductive stabilization.[33] Dihydropyrans customarily exhibit greater kinetic acidities than dihydrofurans,[10] although the presence of other ring substituents can reverse this trend. These ring size effects, which prevail despite quite small differences in pK_a, have been attributed to the poorer p–π conjugation in 6-membered enol ethers than in 5-membered enol ethers.[38] The relative ease of proton abstraction may well be linked to the prevailing ground-state conformations for these heterocyclic systems (half-chair for 6-membered,[39] envelope for 5-membered[40]) and to the resultant extent of $\sigma^*_{CH\alpha}$ population by the *n* electrons on oxygen.[33] In line with these suggestions, the α-vinylic proton in **41** is deshielded by 0.15 ppm relative to that in **42** (values for $CDCl_3$ solutions).[41]



The ^{1}H NMR spectra of **29** and **30** in the same solvent are characterized by rather pronounced differences in the chemical shift ordering of their three aromatic protons. In benzopyran **30**, the proton adjacent to the ring oxygen atom (labeled as α) appears at lowest field, followed in order by the β and β' protons (see Figure 1). On a comparative basis, the β' proton in benzofuran **29** is greatly affected by the ring contraction and is displaced 0.19 ppm to lower field. Does the resultant switch from an $\alpha > \beta$

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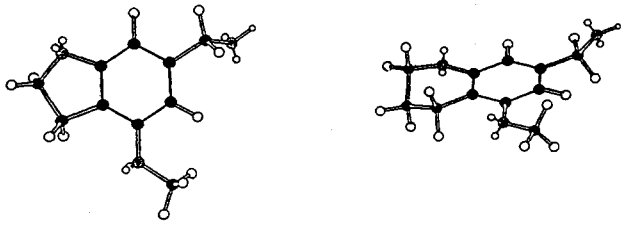
> β' ordering to one in which β' is now most deshielded ($\beta' > \alpha > \beta$) carry with it a suggestion of regioreversed kinetically controlled deprotonation?

The experimental data do indeed demonstrate that H_α in **30** is the most readily labilized. However, the proton distributions indicate $H_{\beta'}$ to be the second most reactive site, thus contraindicating the trend suggested by the respective chemical shifts. Where **29** is concerned, the most downfield proton ($H_{\beta'}$) emerges as the kinetically most acidic. Accordingly, ^{1}H NMR *may* serve as an indicator of reactivity. Caution must be applied, however, since inductive effects are not uniquely contributory to chemical shift.

The differing regioselectivities observed for the lithiations of **29** and **30** bring to light the fact that ether oxygen atoms contained in differently sized rings can indeed exhibit different levels of control on the site of kinetic metalation. While the ring oxygen in these systems is conformationally locked, the CH_3O substituent is not at all inhibited from rotating freely. The latter feature is of importance, and the behavior of **9** and **19** dramatically demonstrates the consequences of sterically impeding this process. In this pair of alcohols, the methoxyl group populates mainly a ground-state conformation anti to the heterocyclic ring as illustrated in **A** and **B** so as to minimize nonbonded interactions.[42] In this conformation, the



A B

nonbonded electron pairs on the methoxyl oxygen cannot be readily canted in the direction of H_β. In contrast, those associated with the ring oxygens are constrained to bisecting or eclipsing H_α. The inability of methoxyl oxygen to engage substantively in resonance is revealed in the ^{1}H NMR spectra of both **19** (H_α, δ 6.45; H_β, δ 6.29) and **9** (H_α, δ 6.58; H_β, δ 6.34) in C_6D_6 solution. As before, however, the larger O–C–C_α angle associated with the reduced size of the dihydrofuran ring (127.4°) relative to that in the dihydropyran series (118.9°) causes H_β in **9** to be downfield of that in **19** by 0.05 ppm.

Since the methoxyl group is deprived of the maximum opportunity for *n*-electron delocalization in the ground state,[38,43] somewhat more energy will need to be expended for it to reach the transition state. Consequently, α vs β competition should be more important in the case of benzodihydrofuran, as it actually is. Note, however, that these steric factors are in fact stereoelectronic in nature as the question is once again complexation en route to the transition state.[34b,44] This analysis should not be construed to mean that abstraction of H_β cannot operate. In fact, the conversion of **40** to **8** proceeds with reasonable efficiency. The benzylic oxygen may play a key role in the success of this transformation. The possibility of lithiation in the absence of this directing group has not been investigated.

In summary, the metalations of **29** and **30** with *n*-butyllithium under kinetically controlled conditions proceeds preferentially at that aryl position bonded to the most deshielded proton. Only minor deviations from this trend are seen when TMEDA is added.[45] That two different sites are kinetically favored is indicative that ring size effects on inductive contributions by ether oxygen can be pronounced. In turn, this is reflected in different regioselectivities. This trend can be overridden by sterically impeding the free rotation of a methoxyl group as in **9** and **19**. In these examples, lithiation occurs predominantly ortho to the ring oxygen atom. This regioselectivity allows direct elaboration of lactone **8**, a tricyclic prototype of the austalide DEF subunit.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 1320 and 1600 spectrometers. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz on a Bruker AC-300 instrument. Mass spectra were recorded on a Kratos MS-30 spectrometer at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All solvents were predried by standard methods. All reactions were performed under a dry nitrogen atmosphere.

2,3-Dihydrofuran-5-carboxaldehyde (14).[16] A solution of 2,3-dihydrofuran (30 g, 430 mmol) in anhydrous THF (600 mL) was treated at −78 °C with *tert*-butyllithium in pentane (276 mL, 467 mmol), stirred at this temperature for 20 min, and allowed to warm to 0 °C for 30 min. The reaction mixture was returned to −78 °C, and DMF (60 mL, excess) was slowly introduced. After 1 h, the mixture was quenched with water and diluted with ether. Following acidification with saturated NH_4Cl solution, the product was extracted into ether (3 × 200 mL), and the combined organic phases were washed with saturated $NaHCO_3$ solution and brine prior to drying and evaporation. Flash chromatography of the residue on neutral alumina (elution with 50% ether in petroleum ether) provided 11.6 g (40%) of **14** as a yellow oil.

5,6-Dihydro-4*H*-pyran-2-carboxaldehyde (11). To a cold (−78 °C), stirred solution of dihydropyran (1.00 g, 11.9 mmol) in freshly distilled THF (0.5 mL, 6.0 mmol) was added dropwise 7.70 mL of a 1.7 M solution of *tert*-butyllithium in pentane. After 10 min at that temperature, the reaction mixture was stirred at 0 °C for 20 min, returned to −78 °C, and treated with DMF (1.31 g, 18.0 mmol). After 1 h of stirring at −78 °C, the solution was warmed slowly to rt, treated with saturated NH_4Cl solution, and diluted with ether (15 mL) and water. The aqueous layer was extracted with ether (2 × 15 mL). The combined organic extracts were washed with brine, dried, and concentrated. The residue was chromatographed on alumina (ether elution) to give 0.69 g (46%) of **11** as a colorless oil: IR (neat, cm^{-1}) 1691, 1633, 1408, 1308, 1239, 1175; ^{1}H NMR (300 MHz, C_6D_6) δ 8.93 (s, 1 H), 5.23 (dd, J = 8.7, 4.8 Hz, 1 H), 3.59 (t, J = 4.8 Hz, 2 H), 1.68–1.61 (m, 2 H), 1.31–1.23 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 186.0, 153.5, 121.1, 65.8, 21.6, 21.0; MS *m/z* (M^+ − CHO) calcd 83.0497, obsd 83.0501.

1-Ethyl Hydrogen [(*E*)-4,5-Dihydrofurfurylidene]succinate (16). To a suspension of **15** (8.00 g, 20 mmol) in dry benzene (50 mL) was added **14** (2.00 g, 21 mmol,) and the mixture was stirred at rt for 3 days, freed of solvent under reduced pressure, and subjected to flash chromatography on deactivated (2.4% H_2O added) silica gel (elution with 50% ethyl acetate in petroleum

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ether). There was obtained 1.90 g (40%) of **16** as pale yellow crystals: mp 91 °C; IR ($CHCl_3$, cm^{-1}) 3500, 1730, 1650; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1 H) 5.40 (t, J = 3.2 Hz, 1 H), 4.42 (t, J = 9.5 Hz, 2 H), 4.22 (q, J = 7.1 Hz, 2 H), 3.85 (s, 2 H), 2.71 (dt, J = 3.2, 9.5 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 177.2, 167.5, 154.5, 129.0, 123.8, 111.6, 70.6, 61.2, 33.2, 30.0, 14.1; MS m/z (M^+) calcd 226.0841, obsd 226.0838.

1-Ethyl Hydrogen [[(*E*)-2,3-Dihydro-2*H*-pyran-6-yl]-methylene]succinate (10). To a suspension of **15** (2.70 g, 6.6 mmol) in benzene (20 mL) was added **11** (745 mg, 6.6 mmol). Stirring at 50 °C was maintained until the consumption of aldehyde was complete. Following solvent evaporation, the residual gum was subjected to flash chromatography on deactivated (2.4% H_2O added) silica gel to provide **10** (1.20 g, 76%): IR ($CHCl_3$, cm^{-1}) 1720, 1650; ^1H NMR (300 MHz, C_6D_6) δ 7.19 (br s, 1 H), 4.80 (t, J = 4.2 Hz, 1 H), 4.08 (s, 2 H), 4.00 (q, J = 7 Hz, 2 H), 3.52 (t, J = 5.0 Hz, 2 H), 1.60 (m, 2 H), 1.20 (m, 2 H), 0.96 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 178.2, 167.7, 151.7, 136.6, 122.6, 112.5, 65.7, 61.0, 33.5, 21.6, 21.4, 14.1; MS m/z (M^+) calcd 249.0997, obsd 240.0987.

Ethyl 2,3-Dihydro-4-hydroxy-6-benzofurancarboxylate (17). A solution of **16** (2.90 g, 12.8 mmol) in dry CH_2Cl_2 (100 mL) was treated with oxalyl chloride (1.6 mL, 18 mmol) and heated at reflux for 90 min. The cooled reaction mixture was diluted with water (50 mL), washed with saturated $NaHCO_3$ solution (2 × 10 mL), dried, and evaporated. The residue was purified by flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether) to furnish 2.25 g (85%) of **17** as colorless crystals: mp 188 °C; ^1H NMR (300 MHz, acetone-d_6) δ 7.39 (d, J = 1.2 Hz, 1 H), 7.26 (d, J = 1.0 Hz, 1 H), 4.69 (t, J = 8.8 Hz, 2 H), 4.32 (q, J = 7.1 Hz, 2 H), 3.43 (br s, 1 H), 3.24 (t, J = 8.8 Hz, 2 H), 1.34 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, acetone-d_6) ppm 165.7, 158.1, 156.9, 133.1, 126.3, 115.6, 108.6, 73.0, 61.8, 14.5; MS m/z (M^+) calcd 208.0736, obsd 208.0736.

Ethyl 5-Hydroxy-7-chromancarboxylate (18). Analogous heating of **10** (8.00 g, 33.3 mmol) with oxalyl chloride (3.5 mL, 40 mmol) in CH_2Cl_2 (150 mL) for 90 min and workup provided a crude product that was purified by flash chromatography on silica gel (elution with 30% ethyl acetate in petroleum ether). There was isolated 5.70 g (77%) of **18** as colorless crystals: mp 125 °C; IR ($CHCl_3$, cm^{-1}) 3600, 3400, 1710, 1590, 1430; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 1.6 Hz, 1 H), 7.07 (d, J = 1.6 Hz, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 4.13 (m, 2 H), 2.67 (m, 2 H), 2.00 (m, 2 H), 1.34 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.9, 155.8, 154.4, 129.0, 115.4, 110.4, 107.4, 66.2, 61.1, 21.5, 19.4, 14.2; MS m/z (M^+) calcd 222.0892, obsd 222.0893.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.71; H, 6.36.

2,3-Dihydro-4-methoxy-6-benzofuranmethanol (19). To a cold (0 °C), stirred suspension of NaH (80 mg, 3.3 mmol) in dry THF (10 mL) was added 608 mg (2.29 mmol) of **17** dissolved in 30 mL of THF. After 30 min, methyl iodide (0.50 mL, excess) was introduced, and the reaction mixture was refluxed for 3 h, cooled, poured into ice–water, acidified with 5% HCl, and extracted with ether (3 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 × 10 mL), dried, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) to give the methoxy ester (442 mg, 68%) as a faintly yellow liquid: IR (neat, cm^{-1}) 1730, 1610; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (s, 1 H), 7.11 (s, 1 H), 4.62 (t, J = 8.8 Hz, 2 H), 4.35 (q, J = 7.1 Hz, 2 H), 3.88 (s, 3 H), 3.17 (t, J = 8.8 Hz, 2 H), 1.38 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.5, 161.4, 156.1. 131.8, 119.3, 104.6, 104.0, 78.09, 61.0, 55.6, 27.3, 14.3; MS m/z (M^+) calcd 222.0892, obsd 222.0889.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.75; H, 6.38.

To a slurry of lihtium aluminum hydride (228 mg, 6.0 mmol) in dry THF (50 mL) was added a solution of the methoxy ester (895 mg, 4.0 mmol) in THF (20 mL). The mixture was stirred overnight at rt, carefully quenched with water, poured into 10% HCl, and extracted with CH_2Cl_2 (4 × 20 mL). The combined extracts were dried and concentrated, and the residue was purified by flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether). There was isolated 629 mg (87%) of **19** as a white solid: mp 69 °C; IR ($CHCl_3$, cm^{-1}) 3600, 3500, 1610; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 2 H), 4.61 (s, 2 H), 4.58 (t, J = 8.8 Hz, 2 H), 3.84 (s, 3 H), 3.12 (t, J = 8.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 161.7, 156.6, 142.8, 113.2, 101.7, 101.3, 71.9, 65.6, 55.4, 27.1; MS m/z (M^+) calcd 180.0786, obsd 180.0781.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.69; H, 6.77.

5-Methoxy-7-chromanmethanol (9). O-Methylation of **18** (3.10 g, 14 mmol) with 480 mg (20 mmol) of NaH and 1.60 mL (25 mmol) of methyl iodide in the predescribed manner afforded 2.30 g (70%) of the methoxy ester after flash chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether): colorless crystals; mp 79 °C; IR ($CHCl_3$, cm^{-1}) 1720, 1590, 1460, 1425; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 1.3 Hz, 1 H), 7.07 (d, J = 1.3 Hz, 1 H), 4.34 (q, J = 7.1 Hz, 2 H), 4.15 (t, J = 5.1 Hz, 2 H), 3.86 (s, 3 H), 2.68 (t, J = 6.6 Hz, 2 H), 1.98 (m, 2 H), 1.37 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 166.6, 157.8, 155.4, 129.2, 116.5, 111.2, 102.4, 66.1, 60.9, 55.6, 21.5, 19.6, 14.3; MS m/z (M^+) calcd 236.1049, obsd 236.1050.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 66.09; H, 6.83. Found: C, 65.95; H, 6.89.

Reduction of this substance (2.30 g, 9.8 mmol) with lithium aluminum hydride (555 mg, 14.6 mmol) in THF (150 mL) as detailed above afforded 1.78 g (94%) of **9** after flash chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether): white solid; mp 54 °C; IR ($CHCl_3$, cm^{-1}) 3620, 1630, 1590, 1470, 1460; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (br s, 2 H), 4.58 (s, 2 H), 4.12 (t, J = 5.3 Hz, 2 H), 3.82 (s, 3 H), 2.63 (t, J = 6.6 Hz, 2 H), 1.96 (m, 2 H), 2.73 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.2, 155.6, 140.1, 110.5, 107.9, 100.5 66.1, 65.4, 55.4, 21.8, 19.1; MS m/z (M^+) calcd 194.0942, obsd 194.0942.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.12; H, 7.41.

Generalized Formylation Protocols. Procedure A. A solution of **19** (89 mg, 0.49 mmol) in anhydrous benzene (5 mL) was treated with *n*-butyllithium (0.68 mL of 1.6 M in hexanes, 1.09 mmol) at 20 °C, stirred for 60 min, and treated with 0.5 mL (excess) of DMF (or *N*-formylpiperidine). After 30 min, water and ether were introduced, and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic phases were washed with brine and concentrated. The residue was chromatographed on silica gel to give a combined 70 mg (69%) of **20** and **23** in a ratio of 77:23.

Procedure B. A solution of **19** (114 mg, 0.63 mmol) in ether (5 mL) containing 0.2 mL of TMEDA was treated with *n*-butyllithium (0.87 mL of 1.6 M in hexanes, 1.39 mmol) and stirred for 60 min. DMF (or *N*-formylpiperidine, 0.5 mL, excess) was introduced, followed 30 min later with water. After dilution with ether and subsequent extraction of the aqueous phase with ether (3 × 10 mL), the combined organic layers were washed with brine, dried, and concentrated. The residue was purified chromatographically (silica gel, elution with 50% ethyl acetate in petroleum ether) to give a combined 81 mg (62%) of **20** and **23** in a ratio of 78:22.

Aldehydes **20** and **23** (series **a** and **b**) were notably unstable and were not further characterized.

7-Formyl-5-methoxy-2,3-dihydrobenzofuran (31a): yellow crystals; mp 77.5–78.5 °C; IR (film, cm^{-1}) 1672, 1619, 1485, 1467, 1424; ^1H NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1 H), 7.13 (s, 1 H), 6.86 (s, 1 H), 4.53 (t, J = 8.6 Hz, 2 H), 3.85 (s, 3 H), 3.21 (t, J = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 189.3, 157.6, 154.2, 136.1, 124.5, 109.2, 106.9, 71.1, 56.5, 30.7; MS m/z (M^+) calcd 178.0630, obsd 178.0627.

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.11; H, 5.64.

6-Formyl-5-methoxy-2,3-dihydrobenzofuran (34a): yellow crystals; mp 53.5–56.0 °C; IR (film, cm^{-1}) 1664, 1609, 1484, 1464; ^1H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1 H), 7.00 (s, 2 H), 4.67 (t, J = 9.0 Hz, 2 H), 3.76 (s, 3 H), 3.18 (t, J = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 188.1, 157.5, 154.0, 131.0, 120.0, 118.4, 106.9, 72.6, 55.8, 28.8; MS m/z (M^+) calcd 178.0630, obsd 178.0630.

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.33; H, 5.84.

2,3-Dihydro-5-methoxy-4-benzofurancarboxaldehyde (37a): yellow needles; mp 91.5–92.5 °C; IR (film, cm^{-1})

1672, 1609, 1472, 1450; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.48 (s, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 6.71 (d, J = 8.7 Hz, 1 H), 4.55 (t, J = 8.8 Hz, 2 H), 3.84 (s, 3 H), 3.47 (t, J = 8.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 190.7, 156.6, 154.5, 129.2, 121.6, 114.9, 110.8, 72.0, 56.3, 30.8; MS m/z (M^+) calcd 178.0630, obsd 178.0632.

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.43; H, 5.66.

6-Methoxy-8-chromancarboxaldehyde (31b): white powder; mp 74.5–75.2 °C; IR (film, cm^{-1}) 1676, 1611; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1 H), 7.19 (s, 1 H), 6.61 (s, 1 H), 4.23 (t, J = 5.1 Hz, 2 H), 3.81 (s, 3 H), 2.79 (t, J = 6.5 Hz, 2 H), 2.02 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 189.8, 153.0, 152.8, 125.3, 124.5, 123.9, 108.4, 67.0, 55.9, 25.1, 22.1; MS m/z (M^+) calcd 192.0786, obsd 192.0786.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.55; H, 6.49.

6-Methoxy-7-chromancarboxaldehyde (34b): yellow crystals; mp 60.5–61.5 °C; IR (film, cm^{-1}) 1678, 1618; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 6.82 (d, J = 3.2 Hz, 1 H), 4.21 (t, J = 5.2 Hz, 2 H), 3.73 (s, 3 H), 2.77 (t, J = 6.5 Hz, 2 H), 2.00 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 189.5, 152.7, 152.5, 125.0, 124.1, 123.6, 108.1, 66.7, 55.6, 24.8, 21.8; MS m/z (M^+) calcd 192.0786, obsd 192.0784.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.79; H, 6.33.

6-Methoxy-5-chromancarboxaldehyde (37b): yellow crystals; mp 57.0–59.0 °C; IR (film, cm^{-1}) 1672, 1590; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.54 (s, 1 H), 6.96 (d, J = 9.0 Hz, 1 H), 6.75 (d, J = 9.0 Hz, 1 H), 4.07 (t, J = 4.9 Hz, 2 H), 3.82 (s, 3 H), 3.07 (t, J = 6.5 Hz, 2 H), 1.91 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 192.1, 157.6, 148.9, 124.6, 123.4, 122.6, 110.6, 65.7, 56.1, 23.7, 22.0; MS m/z (M^+) calcd 192.0786, obsd 192.0777.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.99; H, 6.36.

Representative Carboxylation Procedure. A solution of **19** (112 mg, 0.62 mmol) and TMEDA (0.2 mL) in ether (20 mL) was treated with n-butyllithium (0.85 mL of 1.6 M in hexanes, 1.37 mmol) at 20 °C, stirred for 60 min, and transferred via cannula onto powdered dry ice at −30 °C. The reaction mixture was allowed to warm to rt, diluted with CH_2Cl_2, acidified with 10% HCl, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried, and concentrated. [When esterification was performed, the impure carboxylic acids were covered with ether and treated with excess ethereal diazomethane at 0 °C.] The residue was purified chromatographically on silica gel (elution with 50% ethyl acetate in petroleum ether) to give 57 mg (27%) of lactone **21a** and 14 mg (6%) of lactone **24a**. [For separation of the methyl esters, the elution solvent consisted of 25% ethyl acetate in hexanes.]

3,6-Dihydro-4-methoxybenzo[2,1-*b*:3,4-*c*']difuran-8(2*H*)-one (21a): colorless crystals; mp 197 °C; IR ($CHCl_3$, cm^{-1}) 1770, 1630; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1 H), 5.18 (s, 2 H), 4.78 (t, J = 8.9 Hz, 2 H), 3.89 (s, 3 H), 3.13 (t, J = 8.9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.8, 161.8, 158.9, 150.0, 115.2, 102.3, 96.2, 74.1, 69.6, 55.9, 26.4; MS m/z (M^+) calcd 220.0736, obsd 220.0736.

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89. Found: C, 64.21; H, 5.11.

3,7-Dihydro-4-methoxybenzo[1,2-*b*:4,5-*c*']difuran-5(2*H*)-one (24a): colorless crystals; mp 111 °C; IR ($CHCl_3$, cm^{-1}) 1760, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 1 H), 5.09 (s, 2 H), 4.68 (t, J = 8.8 Hz, 2 H), 4.13 (s, 3 H), 3.31 (t, J = 8.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.8, 161.6, 156.0, 151.6, 117.2, 108.6, 97.4, 73.0, 68.4, 60.8, 27.3; MS m/z (M^+) calcd 206.0579, obsd 206.0575.

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89. Found: C, 64.47; H, 5.38.

2,3,4,7-Tetrahydro-5-methoxy-9*H*-furo[3,4-*h*]-1-benzopyran-9-one (21b): white crystals; mp 166–168 °C; IR ($CHCl_3$, cm^{-1}) 1760, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1 H), 5.11 (s, 2 H), 4.29 (t, J = 5.1 Hz, 2 H), 3.87 (s, 3 H), 2.61 (t, J = 6.5 Hz, 2 H), 1.99 (s,2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.3, 163.4, 154.5, 148.6, 111.6, 105.7, 94.9, 68.5, 66.7, 55.9, 20.9, 19.1; MS m/z (M^+) calcd 220.0736, obsd 220.0736.

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.39; H, 5.61.

2,3,4,8-Tetrahydro-5-methoxy-6*H*-furo[3,4-*g*]-1-benzopyran-6-one (24b): white crystals; mp 116 °C; IR ($CHCl_3$, cm^{-1}) 1760, 1630, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (s, 1 H), 5.14 (d, J = 6.6 Hz, 2 H), 4.21 (t, J = 5.2 Hz, 2 H), 4.13 (s, 3 H), 2.77 (m, 2 H), 1.99 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.8, 161.5, 158.2, 147.5, 115.9, 108.1, 104.8, 68.6, 66.8, 62.2, 21.2, 19.4; MS m/z (M^+) calcd 220.0736, obsd 220.0733.

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.54; H, 5.63.

Methyl 2,3-dihydro-5-methoxy-4-benzofurancarboxylate (38a): yellowish oil; IR (film, cm^{-1}) 1732, 1465, 1324, 1254, 1230; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, J = 8.7 Hz, 1 H), 6.33 (d, J = 8.7 Hz, 1 H), 4.04 (t, J = 8.7 Hz, 2 H), 3.57 (s, 3 H), 3.36 (s, 3 H), 2.94 (t, J = 8.7 Hz, 2 H); MS m/z (M^+) calcd 208.0735, obsd 208.0729.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.44; H, 5.81. Found: C, 63.76; H, 6.04.

Methyl 6-methoxy-5-chromancarboxylate (38b): white crystals; mp 81.2–84.0 °C; IR (film, cm^{-1}) 1731, 1483, 1349, 1335, 1296, 1264, 1249; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 9.0 Hz, 1 H), 6.34 (d, J = 9.0 Hz, 1 H), 3.66 (t, J = 5.2 Hz, 2 H), 3.61 (s, 3 H), 3.28 (s, 3 H), 2.54 (t, J = 6.5 Hz, 2 H), 1.38 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 167.8, 150.6, 149.6, 124.8, 120.9, 118.5, 111.4, 65.8, 56.1, 51.5, 22.9, 22.0; MS m/z (M^+) calcd 222.0892, obsd 222.0895.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.84; H, 6.35. Found: C, 65.18; H, 6.44.

Representative Procedure for Condensation with Benzaldehyde. A solution of **29** (73 mg, 0.41 mmol) and TMEDA (0.2 mL) in anhydrous ether was treated with n-butyllithium (0.64 mL of 1.4 M in hexanes, 0.89 mmol) at 20 °C, stirred for 60 min, and treated with 0.5 mL (excess) of benzaldehyde, followed 30 min later with water. After dilution with ether and subsequent extraction of the aqueous layer with ether (3 × 10 mL), the combined organic phases were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 50% ethyl acetate in petroleum ether) to furnish 59 mg (50%) of the carbinol mixture as a white solid, mp 99 °C.

2,3-Dihydro-4-methoxy-α^7-phenyl-6,7-benzofurandimethanol (22a): IR ($CHCl_3$, cm^{-1}) 3400, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.42 (s, 1 H), 6.19 (s, 1 H), 4.58 (m, 2 H), 4.46 (m, 2 H), 3.81 (s, 3 H), 3.25 (t, J = 8.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.5, 155.5, 145.6, 139.9, 128.0, 126.7, 125.6, 117.3, 113.4, 105.5, 72.0, 69.0, 63.6, 55.3, 27.2; MS m/z ($M^+ - H_2O$) calcd 256.1099, obsd 256.1066.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.12, H, 6.52.

2,3-Dihydro-4-methoxy-α^5-phenyl-5,6-benzofurandimethanol (25a): IR ($CHCl_3$, cm^{-1}) 3400, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.55 (s, 1 H), 6.27 (s, 1 H), 4.58 (m, 2 H), 4.27 (m, 2 H), 3.60 (s, 3 H), 3.27 (t, J = 8.7 Hz, 2 H); MS m/z ($M^+ - H_2O$) calcd 256.1099, obsd 256.1066.

5-Methoxy-α^8-phenyl-7,8-chromandimethanol (22b): white crystals; mp 52 °C; IR ($CHCl_3$, cm^{-1}) 3600, 3400, 1600, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.23 (m, 5 H), 6.45 (s, 1 H), 6.33 (s, 1 H), 4.47 (d, J = 12.3 Hz, 1 H), 4.30 (d, J = 12.3 Hz, 1 H), 4.13–4.02 (m, 2 H), 3.80 (s, 3 H), 2.66 (dt, J = 2.1, 6.6 Hz, 2 H), 1.96–1.91 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 157.1, 153.4, 144.4, 127.9, 127.9, 126.4, 125.5, 122.0, 111.0, 103.8, 68.5, 66.2, 63.7, 55.3, 21.4, 19.2; MS m/z (M^+) calcd 300.1361, obsd 300.1377.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.71; H, 7.01.

5-Methoxy-α^6-phenyl-6,7-chromandimethanol (25b): IR ($CHCl_3$, cm^{-1}) 3400, 1610; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 6.59 (s, 1 H), 6.31 (s, 1 H), 4.32 (m, 2 H), 4.13–4.02 (m, 2 H), 3.61 (s, 3 H), 2.25 (m, 2 H), 2.00 (m, 2 H); MS m/z (M^+) calcd 300.1361, obsd 300.1377.

Representative Procedure for Condensation with Monomeric Formaldehyde. A solution of **29** (1.00 g, 6.1 mmol) and TMEDA (1.42 g, 12.2 mmol) in anhydrous ether (10 mL) was treated with 1.0 equiv of n-butyllithium at rt, stirred for 90 min, and treated with excess monomeric formaldehyde as a freshly distilled solution in THF. After 45 min, water was introduced, and the solution was brought to pH 7 with 2 N HCl. The aqueous

layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried, and evaporated to yield a clear oil. Column chromatography on silica gel (elution with 25% ethyl acetate in hexanes) yielded the purified mixture of products.

General Procedure for Aldehyde Reduction. A solution of **31** (50 mg, 0.260 mmol) in absolute ethanol (6 mL) was treated with sodium borohydride (10 mg, 0.260 mmol), stirred for 5 min, quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed with brine, dried, and evaporated. The residual white solid was sublimed in vacuo.

2,3-Dihydro-5-methoxy-7-benzofuranmethanol (33a): 77% yield; yellowish semisolid; IR (film, cm^{-1}) 3407, 2932, 1601, 1462, 1425, 1192, 1157, 1042, 943, 869, 737; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1 H), 6.73 (s, 1 H), 4.60 (s, 2 H), 4.54 (t, J = 8.5 Hz, 2 H), 3.81 (s, 3 H), 3.19 (t, J = 8.5 Hz, 2 H), 2.20 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 153.8, 151.8, 128.6, 126.5, 109.6, 107.9, 71.2, 62.2, 56.0, 30.4; MS m/z (M^+) calcd 180.0786, obsd 180.0779.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72. Found: C, 66.66; H, 6.86.

2,3-Dihydro-5-methoxy-6-benzofuranmethanol (36a): 68% yield; white crystals; mp 54.5–56.0 °C; IR (film, cm^{-1}) 3412, 1482, 1183, 1139, 1045, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, J = 2.4 Hz, 1 H), 6.55 (d, J = 2.7 Hz, 1 H), 4.62 (s, 2 H), 4.56 (t, J = 2.4 Hz, 2 H), 3.75 (s, 3 H), 3.17 (t, J = 8.6 Hz, 2 H), 2.36 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 154.1, 141.6, 127.9, 122.5, 111.7, 110.6, 71.4, 61.1, 56.0, 30.0; MS m/z (M^+) calcd 180.0786, obsd 180.0788.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72. Found: C, 66.92; H, 6.90.

6-Methoxy-8-chromanmethanol (33b): 100% yield; white crystals; mp 83.5–85.0 °C; IR (film, cm^{-1}) 3500–3000, 3000–2900, 1482, 1218, 1150, 1041, 863, 828; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (d, J = 3 Hz, 1 H), 6.54 (d, J = 3 Hz, 1 H), 4.61 (s, 2 H), 4.19 (t, J = 5.0 Hz, 2 H), 3.74 (s, 3 H), 2.78 (t, J = 2 Hz, 2 H), 2.23 (s, 1 H), 2.00 (dt, J = 4, 2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 152.8, 146.9, 129.2, 122.8, 113.7, 112.5, 66.5, 62.2, 55.7, 25.0, 22.4; MS m/z (M^+) calcd 194.0943, obsd 194.0944.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.01; H, 7.27. Found: C, 67.65; H, 7.29.

6-Methoxy-7-chromanmethanol (36b): 82% yield; yellowish semisolid; IR (film, cm^{-1}) 3419, 1418, 1199, 1064; ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1 H), 6.54 (s, 1H), 4.59 (s, 2 H), 4.13 (t, J = 5.0 Hz, 2 H), 3.80 (s, 3 H), 2.77 (t, J = 6.5 Hz, 2 H), 2.00 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 151.1, 148.6, 128.3, 121.6, 117.1, 111.4, 66.3, 62.0, 55.7, 25.0, 22.4; MS m/z (M^+) calcd 194.0943, obsd 194.0944.

General Procedure for Ester Reduction. A solution of **38a** (30 mg, 0.135 mmol) in dry ether (3 mL) was added dropwise to a magnetically stirred slurry of $LiAlH_4$ (5 mg, 0.135 mmol) in the same solvent (1 mL). The reaction mixture was stirred for 32 min, quenched with water, and acidified to pH 1 with 5% H_2SO_4. The solution was extracted with ether (3 × 20 m), and the combined organic layers were washed with brine, dried, and evaporated to leave a white solid which was purified chromatographically (silica gel, elution with 40% ethyl acetate in hexanes).

2,3-Dihydro-5-methoxy-4-benzofuranmethanol (39a): 90% yield; off-white crystals; mp 62.0–63.5 °C; IR (film, cm^{-1}) 3416, 1714, 1606, 1462, 1230, 1073; ^1H NMR (300 MHz, $CDCl_3$) δ 6.65 (s, 2 H), 4.65 (s, 2 H), 4.55 (t, J = 8.6 Hz, 2 H), 3.82 (s, 3 H), 3.23 (t, J = 8.6 Hz, 2 H), 1.26 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 154.1, 152.2, 127.3, 125.6, 109.9, 107.9, 71.4, 59.5, 56.2, 28.8+; MS m/z (M^+) calcd 180.0786, obsd 180.0784.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72. Found: C, 66.89; H, 6.93.

6-Methoxy-5-chromanmethanol (39b): 91% yield; white solid; mp 74.2–75.5 °C; IR (film, cm^{-1}) 3355, 2932, 1654, 1485, 1301, 1254, 1091, 1039, 800; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, J = 3.9 Hz, 2 H), 4.69 (s, 2 H), 4.10 (t, J = 5.2 Hz, 2 H), 3.81 (s, 3 H), 2.86 (t, J = 6.6 Hz, 2 H), 2.10 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 151.7, 149.3, 127.3, 122.0, 116.5, 110.1, 65.7, 56.8, 56.0, 22.3, 22.1; MS m/z (M^+) calcd 194.0943, obsd 194.0943.

5-Methoxy-8-methyl-7-chromanmethanol (40). A mixture of **20b** (373 mg, 1.68 mmol), hydrazine hydrate (8.40 g, 169 mmol), and K_2CO_3 (8.40 g, 60 mmol) in diethylene glycol (20 mL) was heated at 180 °C for 4 h and at 150 °C overnight. The cooled mixture was diluted with water (20 mL) and extracted with ether (3 × 30 mL). The combined organic phases were washed with 10% HCl (2 × 20 mL) prior to drying and solvent evaporation. Flash chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether) gave 210 mg (60%) of **40** as a white powder: mp 89 °C; IR ($CHCl_3$, cm^{-1}) 3620, 1620, 1590, 1460, 1430; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 4.65 (s, 2 H), 4.16 (t, J = 5.1 Hz, 2 H), 3.81 (s, 3 H), 2.66 (t, J = 6.6 Hz, 2 H), 2.11 (s, 3 H), 1.95 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 155.7, 153.7, 137.11, 116.0, 110.5, 101.2, 66.2, 62.8, 55.4, 21.8, 19.4, 10.2; MS m/z (M^+) calcd 208.1099, obsd 208.1096.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.77.

2,3,4,8-Tetrahydro-5-methoxy-9-methyl-6*H*-furo[3,4-*g*]-1-benzopyran-6-one (8). To a solution of **40** (276 mg, 1.33 mmol) and TMEDA (0.5 mL) in anhydrous ether (50 mL) was added *n*-butyllithium (2.10 mL of 1.4 M in hexanes, 2.92 mmol). After 60 min, the mixture was poured onto powdered dry ice and worked up after reaching rt. There was obtained 31 mg of **8** and 142 mg (51%) of recovered **40**. The yield of **8** based on recovered starting material was 21%: white solid; mp 149 °C; IR ($CHCl_3$, cm^{-1}) 1760, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 2 H), 4.25 (t, J = 5.2 Hz, 2 H), 4.09 (s, 3 H), 2.78 (t, J = 6.5 Hz, 2 H), 2.03 (s, 3 H), 2.00 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.4, 158.8, 156.1, 145.6, 115.7, 114.1, 107.4, 68.2, 66.9, 62.1, 21.2, 19.6, 10.7; MS m/z (M^+) calcd 234.0892, obsd 234.0888.

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 67.03; H, 6.46.

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Supplementary Material Available: ^1H NMR spectra of **10, 16, 17, 25a, 25b, 36b,** and **39b** (7 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.