Neighboring Group Effects in Intramolecular Aldol Condensations. Rate Enhancement by γ Substituents[1]

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The *O*-acetyl dieneol **1b**, obtained from the Grignard addition of 2-(2-bromoethyl)-1,3-dioxolane to 2,4-hexadienal via **1a**, and followed by an acetylation, was treated with maleic anhydride to give the crystalline Diels−Alder adduct **2b** with good stereoselectivity. The acetal of **2b** was selectively hydrolyzed to the acetoxy aldehyde **3b**. This was treated with potassium hydride in tetrahydrofuran. A stereoselective intramolecular Aldol reaction resulted in the formation of the tricyclic lactone **4b**. However, attempts to achieve an Aldol condensation under similar reaction conditions with the analogous aldehyde **3c**, lacking the acetoxy group, failed, giving back the starting material **3c**. On the other hand, the methoxy aldehyde **3d** was cyclized to the tricyclic compound **4d**.

The Diels−Alder[2] reaction represents a powerful tool for the preparation of six-membered ring systems containing up to four stereogenic centers on the cyclohexene ring. In the case of the intramolecular reaction,[3] a stereogenic center may connect the diene with the dienophile and control the generation of the new stereogenic centers. In the case of the intermolecular[4] reaction, stereogenic centers may be built into one or both of the components. Due to the nature of these reactions, one might expect a lower stereoselectivity in most cases.

Our interest[5] in the regio- and stereoselectivity of intramolecular Diels−Alder reactions of fumarates has prompted this investigation regarding similar but intermolecular cycloaddition reactions with maleic anhydride. In order to avoid a reaction between the dienophile and the hydroxy group of the diene, the latter had to be protected. This paper describes a novel approach to an octalinic system, whose rate of formation is strongly enhanced by substituents placed in the vicinity of the reaction centers.

The Grignard reagent,[6] prepared from 3-bromopropionaldehyde ethylene acetal[7] at a temperature not exceeding 30 °C, was treated with sorbic aldehyde.[7] The magnesium salt of the hydroxy diene acetal[5] **1a** thus obtained was directly acetylated with acetic anhydride in a one-pot procedure. The resulting acetate **1b** was isolated in 30% yield following chromatography on silica gel. According to the 360 MHz NMR spectrum of **1b**, the diene acetate consisted of a mixture of isomers. The acetate methyl group gave rise to two barely resolved singlets (estimated ratio 4:1) near δ 2.05, indicating the presence of double-bond isomers, originating in all likelihood from the sorbic aldehyde.

The acetoxy diene **1b** was heated for up to 9 h in the presence of 2 equiv of maleic anhydride in refluxing toluene (Scheme 1). When the progress of the cycloaddition reaction was followed by thin layer chromatography, it was noticed that material corresponding to the diene acetate **1b** was still present despite the use of an excess of maleic anhydride. This would support the above observation that the diene **1b** was not isomerically pure and that only the all-trans isomer would undergo a Diels−Alder reaction with maleic anhydride. The crude cycloaddition product was chromatographed on silica gel. The purified compound **2a** was isolated, again judging from its NMR spectra, as a single diastereoisomer in over 70% yield[8] and was readily crystallized from a small amount of ether. The cycloaddition between 5-acetoxy-1,3-heptadiene and maleic anhydride was reported[9] to give in 68% yield two diastereoisomers in a ratio of 1.8:1.

Proton NMR spectroscopy of **2b** in pyridine confirmed the assigned stereochemistry of the cyclohexene ring formed during the Diels−Alder addition. Strong 1,4-NOE interactions were observed between the two allylic protons, indicative of a 1,4-cis-disubstituted cyclohexene expected from a trans,trans diene. Two, albeit weaker, 1,3-effects were discernible between the allylic protons and the two protons introduced into the molecule by the maleic anhydride, respectively. These facts point to the presence of an all-cis-substituted boat conformation for the unsaturated carbocyclic ring in **2b** as expected from the endo transition state for the Diels−Alder reaction.

The relative stereochemistry of the fifth, exocyclic stereogenic center of compound **2b** was deduced from the product of the following sequence of reactions: The acetal **2b** was hydrolyzed in the presence of *p*-toluenesulfonic acid to the aldehyde **3b**. This was obtained as a crystalline product in 71% yield. When the aldehyde **3b** was treated with sodium hydride in tetrahydrofuran, the starting material was recovered unchanged. However,

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(2) (a) Holmes, H. L. *Organic Reactions*; Wiley: New York, 1948; Vol. 4, p 60. (b) Kloetzel, M. C., ref 2a, p 1. (c) Butz, L. W.; Rytina, A. F., ref 2a, 1949; Vol. 5, p 136. (d) Klein, O. *Methoden Org. Chem. (Houben-Weyl)* **1972**, 5/*1b*, 433. (e) Wollweber, H. *Ibid.* **1970**, *5/1c*, 977.

(3) Ciganek, E. *Organic Reactions*; Wiley: New York, 1984; Vol. 32, p 1.

(4) (a) Carlson, R. G. *Annu. Rep. Med. Chem.* **1974**, *9*, 270. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (c) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.

(5) Eberle, M. K.; Weber, H.-P. *J. Org. Chem.* **1988**, *53*, 231.

(6) Büchi G.; Wüest H. *J. Org. Chem.* **1969**, *34*, 1122.

(7) Commercial product.

(8) Taking into consideration that the diene **1b** was estimated to be a 4:1 mixture of double-bond isomers, the conclusion may be allowed that the cycloaddition is proceeding with a diastereoselectivity of 90% or better. It has not escaped our attention that the diene acetate **2b** might undergo a series of allylic rearrangements with concomitant 1,3-migrations of the acetate, thus alleviating the problem of double-bond isomers (see also ref 5). Judging from our experimental results, it may be concluded that the reaction conditions were not conducive to such rearrangements.

(9) Hamada, T.; Sato, H.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1989**, *30*, 6405.

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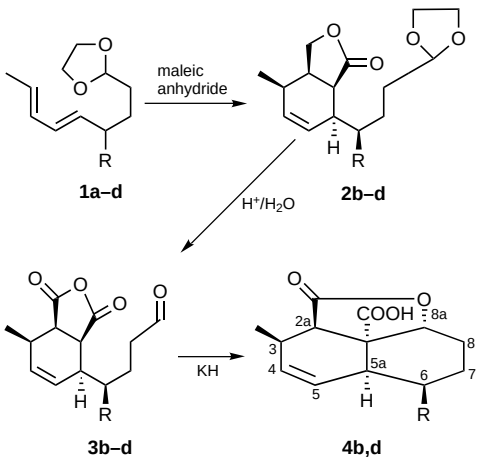
Scheme 1[a]



[a] **a**, R = OH; **b**, R = OAc; **c**, R = H; **d**, R = OCH_3.

after the aldehyde **3b** was treated with slightly more than 1 equiv of potassium hydride in absolute tetrahydrofuran for 2 days at room temperature, a stereoselective intramolecular Aldol[10] condensation was observed. The crystalline product was isolated in 64% yield and was assigned the structure and the stereochemistry of the tricyclic acid **4b**. The acidic character of the cyclization product was also ascertained through treatment with diazomethane, leading to the formation of the methyl ester of **4b** according to mass spectral and NMR data obtained for this product.

Both the assignments for the structure and the stereochemistry of the product **4b** were based upon ^{13}C and ^{1}H NMR data obtained for this compound. In the ^{13}C NMR spectrum, each carbon atom present in **4b** gave rise to one distinct signal as expected for a single diastereoisomer. It immediately became obvious that the product was lacking the aldehyde function. Among the building blocks of the new molecule, 11 protonated carbons were counted. These in turn could be assigned to two methyl groups, two methylene groups, and seven methine carbons. The group of methines included the two double-bond carbons, three methines bearing carbon substituents only, and two methines, each substituted with one oxygen atom and observed at 70.4 and 78.7 ppm. The signal of the acetate-substituted carbon at 70.4 ppm had undergone a small upfield shift in comparison to its precursors **2b** (72.0 ppm) and **3b** (71.8 ppm). With the two methylene groups still present in **4b**, the peak at 78.7 ppm was assigned to the carbon that was derived from the former aldehyde carbon now substituted with one additional carbon atom. Three signals in the region of 170 ppm were assigned to the acetate, lactone, and acid carbonyl carbons. Lastly and most significantly, the carbon not yet accounted for was now found to be fully substituted by four carbon atoms (53.6 ppm). From the fully coupled proton NMR spectrum of **4b**, the following coupling constants were measured directly: (1) the proton attached[11] to the carbon 3 (δ 2.75 ppm) had one coupling constant of $J = 7.6$ Hz to the methyl group and another of $J = 11.2$ Hz to the proton at position **2a** (δ 3.24 ppm) and (2) the axial proton at position 8a (δ 4.45 ppm) had coupling constants of $J = 11.2$ Hz and $J = 5.3$ Hz to the axial and equatorial protons at position 8 (δ 2.1 ppm), respectively. Decoupling experiments were performed with **4b** in $CDCl_3$ by systematically irradiating at those positions giving rise to signals due to one or more protons. This allowed the assignment of all the stereogenic centers of acid **4b**. The most valuable information regarding coupling constants was gained from a single experiment by irradiating in the region of 2.1 ppm. Here, the signals due to three protons were detected: the equatorial proton at position 7 and the two protons at position 8. In the decoupled spectrum, the signal due to the axial proton at position 8a (δ 4.45 ppm) had collapsed to a singlet. The previously broad signal assigned to the axial proton at position 7 (δ 1.5 ppm) had collapsed to a slightly broadened doublet ($J = 10.7$ Hz) still coupled to the axial proton at position 6 while the signal centered at δ 5.35 ppm and assigned to the axial proton at position 6 appeared now as a doublet of doublets with measured coupling constants of $J = 6.1$ and $J = 11.0$ Hz, respectively. While the larger of the two values was found, within the limits of error, to be identical with the aforementioned coupling between the axial proton at position 7 and the axial proton at position 6 ($J = 10.7$ Hz; see above), the smaller value of 6.1 Hz was assigned to the coupling constant between the protons at positions 5a and 6, indicating a cis stereochemistry for the two carbocyclic rings. Upon irradiation in the region of δ 1.5 ppm, the pattern in the 5.3 ppm region showed the presence of only small residual coupling, representing additional support for the assignment of a cis octalin system. Irradiating at the frequency due to the proton at the carbon 5a (δ 3.4 ppm) allowed verification of the coupling constants of $J = 5$ and $J = 12$ Hz between the axial proton at the position 6 and the equatorial and axial protons at position 7, respectively. The coupling constants are summarized in Table 1.

The stereochemical assignment of compound **4b** was further supported by nuclear Overhauser experiments (NOE). The following through-space interactions were observed experimentally: between the axial proton at C-8a and both the axial proton at C-7 and the methyl group at C-3 and also between the axial proton at C-6 and the axial proton at C-8. However, no interactions were detectable between the two allylic protons at C-5a and C-3. This seems to indicate the presence of a rigid envelope conformation for the unsaturated ring in **4b**.

In retrospect, the stereochemistry deduced for the tricyclic compound **4b** allowed the assignment of the relative stereochemistry to both its precursors **2b** and **3b** (see above).

With the intention of carrying out a similar sequence of reactions in order to prepare the analog of **4b** lacking, however, the acetoxy group, the Grignard reagent prepared above was also allowed to react with the known[12] 1-chloro-2,4-hexadiene (from sorbic alcohol in the presence of thionyl chloride). This led, in 35% yield, to the acetal of 5,7-nonadienal **1c.** The latter underwent a Diels–Alder reaction with maleic anhydride in 98% yield. The product **2c** of this cycloaddition reaction was crystallized from ether and fully characterized by ^{1}H and ^{13}C NMR spectroscopy (see Experimental Section). Hydrolysis under acidic conditions led to the cleavage of the acetal protecting group, forming the well-defined crystalline aldehyde **3c**. A compound with an ester in place of

(10) (a) Mukaiyama T. *Organic Reactions*; Wiley: New York, 1982; Vol. 28, p 203. (b) Nielson, A. T.; Houlihan, W. J. *Organic Reactions*; Wiley: New York, 1968; Vol. 16, p 1.

(11) For the numbering of **4b**, see Scheme 1.

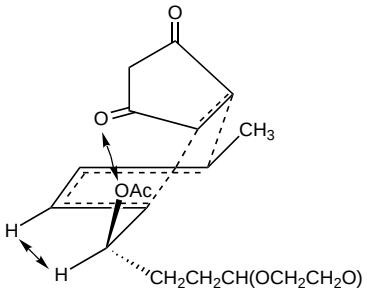
(12) Maginiac, P. *Ann. Chim.* **1962**, *7*, 445; *Chem. Abstr.* **1963**, *58*, 6681h.

Table 1. Compound 4b in $CDCl_3$. Chemical Shifts (δ) and H−H Coupling Constants (Hz)[q]

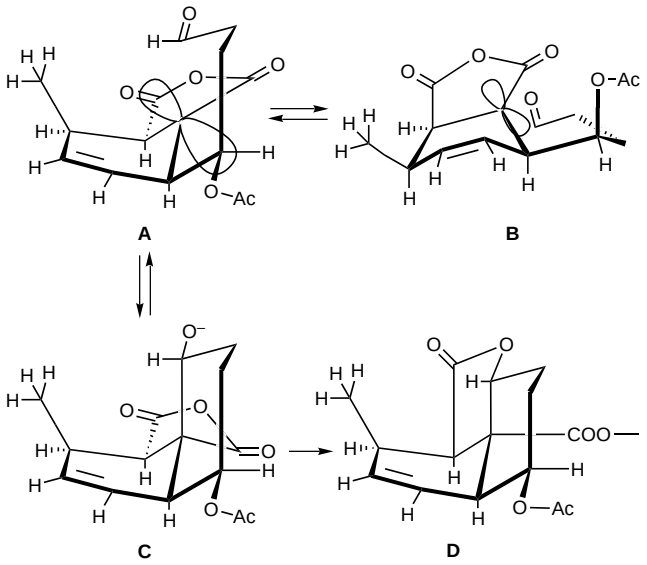
	H_{2a}	H_3	H_4	H_5	H_{5a}	H_6	H_{7ax}	H_{7eq}	H_{8ax}	H_{8eq}	H_{8a}	CH_3C^3
H_{2a}	*3.20*	11.2										
H_3		*2.75*	3	3								7.6
H_4			*5.88*	11	3							
H_5				*5.78*	s[b]							
H_{5a}					*3.37*	6.1						
H_6						*5.35*	10.7	5.7				
H_{7ax}							*1.52*					
H_{7eq}						11.45		*2.10*				
H_{8ax}									*2.10*		11.2	
H_{8eq}										*2.10*	5.3	
H_{8a}											*4.42*	
CH_3C^3												*1.22*

[a] Chemical shifts are in italics. [b] s = small.

Chart 1



Scheme 2



the aldehyde **3c** has been described[13] and was prepared in a similar way. Compound **3c** was subjected to the same conditions that led to the formation of **4b** from **3b**: potassium hydride in absolute tetrahydrofuran at room temperature for as long as 3 days. In this case, however, the starting material was recovered unchanged following several attempts to cyclize the aldehyde **3c**.

Intrigued by fact that the Diels−Alder product without the acetoxy group did not undergo an intramolecular aldol condensation in the presence of potassium hydride, the acetoxy group was next replaced by a methoxy group. This was accomplished by the following sequence of reactions. Treatment of **1a**[5] with sodium hydride and methyl iodide gave the methoxy diene **1d**. This was treated with maleic anhydride to give the crystalline Diels−Alder product **2d** in 38% yield as a single diastereoisomer. Following acidic hydrolysis of the acetal protecting group, the crystalline aldehyde **3d** underwent cyclization to the acidic lactone **4d** in the presence of potassium hydride. The NMR spectra of the acidic methoxy lactone **4d** and the acetoxy lactone **4b** were found to be very similar, thus suggesting the presence of the same carbon skeleton.

Mechanistic Considerations. The formation of the diastereoisomer **2b** may be explained by assuming a transition state as shown in Chart 1. In the usual endo transition state the incoming maleic anhydride should be subjected to the influence of the nearby stereogenic center of the diene acetate. If in the transition state the acetoxy group were to assume an antiperiplanar position with respect to the diene double bonds, the dienophile could approach the diene from the less hindered side of the proton. On the other hand, a transition state featuring the smallest possible periplanar interaction by the two protons highlighted in Chart 1 due to 1,3-allylic ($A_{1,3}$) strain[14] might be favored. In this case the dienophile would approach the diene from the less hindered side of the substituted oxygen and in preference over an approach from the direction of the side chain methylene group. Furthermore, in this rotamer the oxygen substituent would be rotated by approximately 30° from the perpenticular position with respect to the plane of the diene, while at the same time bringing the proton into the plane of the diene. It has been reported[15] that the axial conformation of N-substituted allylic amino cyclohexenes was found by X-ray crystallography to be more stable than the equatorial conformation. Thus, a transition state as indicated above might be favored as well. A minimal rotation about the ═CH−CH(OAc) single bond of approximately 30° would move the diene from its hypothetical ground state to the transition state, suitable for the Diels−Alder condensation.

The observations concerning the cyclization of **3b** to **4b** might best be explained by assuming deprotonation of **3b** to occur next to one of the two anhydride carbonyls. The intermediate **B** (see Scheme 2), with the carbanion next to the carbonyl closer to the acetyl substituent and accessible via inversion of the carbanion **A**, could then undergo a stereoselective addition reaction to the aldehyde function, forming the cis octalin **C** bearing an equatorial hydroxylate anion. Further stabilization could be achieved via hydroxylate addition to one of the carbonyl groups of the anhydride, generating at the same time a five-membered lactone and a carboxylate anion

(13) Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 5960.
(14) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(15) Magnus, P.; Lacour, J.; Bauta, W.; Mugrage, B.; Lynch, V. J. *Chem. Soc., Chem. Commun.* **1991**, 1362.

D. Inspection of models illustrated the favorable steric arrangement[16] for the interaction of the intermediary hydroxylate anion of **C** with the carbonyl group leading to the γ-lactone. Protonation of **D** would finally give rise to the formation of product **4a**. As an alternative, the generation of the carbonyl α-carbanion in proximity to the methyl group undergoing addition to the aldehyde function could be envisaged. This, however, would lead to the formation of the less likely [1,3,4]bicyclic carbon skeleton. There remained the question about the possible mode of cyclization of the carbanion **A**. The formation of a *trans*-octalin would force the acetoxy group into an axial position on the newly formed cyclohexane ring, generating an unfavorable 1,3-diaxial interaction with one of the carbonyl groups. This would explain the preferred formation of the *cis*-octalin over a *trans*-octalin skeleton. However, these experiments do not shed light on the role played by the acetoxy (or methoxy) group during the reaction in the presence of potassium hydride. Whether the presence of at least one oxygen atom is essential for the Aldol condensation to be successful can only be answered by additional experiments.

Experimental Section

General. Proton and ^{13}C magnetic resonance spectra were measured in deuterated chloroform solutions unless stated otherwise and are recorded in δ values (ppm) relative to TMS (tetramethylsilane) as internal standard. Melting points were not corrected.

4-Acetoxy-5,7-nonadienal Ethylene Acetal (1b). The Grignard reagent[6] was prepared at a temperature not exceeding 30−35 °C from magnesium (24 g, 1 mol) in dry tetrahydrofuran (600 mL) and 2-(2-bromoethyl)-1,3-dioxolane[7] (182 g, 1.0 mol) in dry tetrahydrofuran (200 mL). After 3 h at rt the solution was cooled in an ice bath. A solution of freshly distilled 2,4-hexadienal[7] (96 g, 1.0 mol) in dry THF (200 mL) was added dropwise. The mixture was stirred at rt overnight. The ice-cold solution was treated with acetic anhydride (110 g, 1.08 mol). After 4 h at rt the organic phase was diluted with ether. Saturated NH_4Cl solution was added. The mixture was diluted with water to dissolve the precipitated salts. The neutral aqueous phase was separated and extracted with ether. The combined organic layers were dried over solid K_2CO_3. The solvent was evaporated to give the crude product (240 g). This was chromatographed on silica gel with ether/hexane (1:4) to give the yellow, liquid product (72.4 g) as a 4:1 mixture of isomers (by NMR): yield 30%; *m/z* calcd for $C_{13}H_{20}O_4$ 240, found 241 $[M + 1]^+$; NMR (360) δ 1.6−1.9, 1.74, 2.02/2.03 (4:1), 3.8−3.9, 3.9−4.0, 4.85, 5.25−5.30, 5.4−5.5, 5.55−5.70, 5.90−6.05, 6.15−6.25. Anal. Calcd for $C_{13}H_{20}O_4$ (240): C, 65.0; H, 8.3. Found: C, 65.0; H, 8.4.

5,7-Nonadienal Ethylene Acetal (1c). The Grignard reagent was prepared[6] as above from magnesium (3.6 g, 0.15 mol) and 2-(2-bromoethyl)-1,3-dioxolane[7] (27 g, 0.15 mol) in dry tetrahydrofuran (50 mL). After 3 h at rt the solution was cooled in an ice bath and 1-chloro-2,4-hexadiene[12] (17.4 g, 0.15 mol) was added. After the addition was complete, the mixture was stirred at rt overnight and then diluted with ether. The organic phase was washed with saturated NH_4Cl solution, dried over K_2CO_3, and evaporated. The residue was distilled under high vacuum to give the product (9.5 g) as a yellow liqiud: yield 35%; bp 65−75 °C/0.1 mm; NMR (90) δ 1.4−1.8, 1.71, 2.0−2.3, 3.8−3.9, 4.0−4.1, 4.85, 5.5−6.5.

4-Methoxy-5,7-nonadienal Ethylene Acetal (1d). The acetate **1b** (24 g, 0.1 mol) was added to a solution of NaOH (6 g, 0.15 mol) in methanol (100 mL). The mixture was kept at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in ether and washed with water until neutral and dried over sodium sulfate. The solvent was evaporated. The residue was added to a suspension of NaH (2.4 g, 0.1 mol) in THF (100 mL). After 1 h at room temperature, methyl iodide (17 g, 0.12 mol) was added. The mixture was kept at room temperature overnight. The solvent was evaporated under reduced pressure. Ether was added, and the solution was washed with water until neutral and dried over sodium sulfate. The crude product was used without further purification: NMR (200) δ 1.5−1.8, 1.77, 3.27, 3.45−3.65, 3.74−3.86, 3.88−4.00, 4.88, 5.25−5.4, 5.6−5.8, 5.9−6.2.

4-[3-(1,3-Dioxolan-2-yl)-1-acetoxypropyl]-7-methyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (2b). A solution of **1b** (4.8 g, 20 mmol) and maleic anhydride (4 g, 40 mmol) in toluene (80 mL) was heated to reflux for 5 h. The solvent was evaporated. The residue was dried at 60 °C under high vacuum to give the crude product (6.3 g). This was chromatographed on silica gel with ether as eluent to give the pure product (4.8 g): yield 71%. A sample was crystallized by the addition of a small amount of ether: mp 118−120 °C; *m/z* calcd for $C_{17}H_{22}O_7$ 338, found 338 $[M]^+$; NMR (90) δ 1.47, 1.65−2.1, 2.10, 2.4−2.6, 3.25−3.35, 3.6−3.7, 3.8−3.9, 3.9−4.0, 4.87, 5.45-5.55, 5.8−5.9; ^{13}C NMR 16.2, 21.0, 26.8, 28.6, 30.8, 39.6, 43.0, 45.8, 65.0, 72.0, 103.8, 128.9, 135.9, 169.9 171.0, 171.3; IR 1730 1770, 1840 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O_7$ (338.36): C, 60.3; H, 6.5. Found: C, 59.9; H, 6.6.

4-[3-(1,3-Dioxolan-2-yl)propyl]-7-methyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (2c). A mixture of the diene acetal **1c** (9.6 g, 53 mmol) and maleic anhydride (5.8 g, 59 mmol) in toluene (50 mL) was heated to reflux overnight. The cold solution was filtered and evaporated. The residue was treated with a small amount of ether to give the pure product (14.5 g): yield 98%; mp 114−115 °C; *m/z* calcd for $C_{15}H_{20}O_5$ 280, found 281 $[M + 1]^+$; NMR (90) δ 1.44, 1.5−2.1, 2.1−2.6, 3.2−3.4, 3.7−4.1, 4.88, 5.7−6.0; ^{13}C NMR 16.3, 22.3, 30.5, 30.6, 33.6, 36.0, 45.0, 46.2, 64.9, 104.2, 133.4, 134.7, 171.3; IR 1770, 1840 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_5$ (280.32): C, 64.3; H, 7.1. Found: C, 63.9; H, 7.2.

4-[3-(1,3-Dioxolan-2-yl)-1-methoxypropyl]-7-methyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (2d). A solution of **1d** (4.5 g, 20 mmol) and maleic anhydride (4 g, 40 mmol) in toluene (80 mL) was heated to reflux for 2 h. The solvent was evaporated. The crude product was chromatographed on silica gel with ether/hexane 1:1. The residue was treated with a small amount of cold ether to give the crystalline product (2.37 g): mp 103−104 °C; yield 38%; *m/z* calcd for $C_{16}H_{22}O_6$ 310, found 311 $[M + 1]^+$; NMR (200) δ 1.44, 1.50−2.1, 2.20−2.35, 2.35−2.60, 3.20−3.35, 3.55, 3.8−4.1, 4.92, 5.75−5.88. Anal. Calcd for $C_{16}H_{22}O_6$ (310.35): C, 61.9; H, 7.2; O, 30.9. Found: C, 61.7; H, 7.0; O, 31.1.

4-(3-Formyl-1-acetoxypropyl)-7-methyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (3b). A mixture of the acetal **2b** (7.1 g, 21 mmol) and *p*-toluenesulfonic acid (1 g, 5.8 mmol) in THF (100 mL) and water (100 mL) was heated on the waterbath for 5 h and was then kept at rt overnight. Methylene chloride was added. The organic phase was washed with a 2 N $NaHCO_3$ solution and with water and was dried over K_2CO_3. The solvent was evaporated, and the residue was treated with ether to give the crystalline product (4.2 g): yield 68%; mp 60−62 °C. A sample was chromatographed on silica gel: mp 70−72 °C; *m/z* calcd for $C_{15}H_{18}O_6$ 294, found 251 $[M - 43]^+$ (loss of CH_2CHO); NMR (200) δ 1.45, 1.75−1.95, 2.05, 2.2−2.4, 2.4−2.8, 3.3−3.4, 3.6−3.7, 5.4−5.5, 5.8−6.0, 9.8; ^{13}C NMR 16.2, 21.0, 25.7, 30.8, 39.4, 39.9, 42.9, 45.7, 71.8, 128.6, 136.2, 170.2, 170.9, 171.3, 201.0; IR 1720−1740, 1775, 1840 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_6$ (294.3): C, 61.2; H, 6.1. Found: C, 59.7; H, 6.2.

4-(3-Formylpropyl)-7-methyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (3c). A mixture of the acetal **2c** (7.5 g, 27 mmol) and *p*-toluenesulfonic acid (1.0 g, 6 mmol) in THF (100 mL) and water (50 mL) was stirred at rt overnight. The usual workup in CH_2Cl_2 gave the product (5.1 g): yield 81%; mp 76−77 °C; *m/z* calcd for $C_{13}H_{16}O_4$ 236, found 237 $[M + 1]^+$; NMR (200) δ 1.43, 1.7−2.0, 2.2−2.7, 3.25−3.5, 5.7−5.9, 9.8; ^{13}C NMR 16.3, 20.4, 30.4, 30.6, 36.1, 43.7, 45.0, 46.3, 133.1, 135.1, 171.1, 171.3, 201.5; IR 1715, 1765, 1840

(16) (a) Bürgi, H. B.; Dunitz J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Dunitz J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_4$ (236.7): C, 66.1; H, 6.8. Found: C, 65.95; H, 7.1.

4-(3-Formyl-1-methoxypropyl)-7-methyl-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (3d). A mixture of the acetal **2d** (620 mg, 2 mmol) and *p*-toluenesulfonic acid (400 mg, 2.2 mmol) in THF (20 mL) and water (20 mL) was kept at 50 °C for 5 h. The organic phase was diluted with ether, washed with a 2 N Na_2CO_3 solution and then with water, and dried over Na_2SO_4. The solvent was evaporated, and the residue was treated with a small amount of cold ether to give the crystalline aldehyde (290 mg): yield 55%; mp 111−112 °C; *m*/*z* calcd for $C_{14}H_{18}O_5$ 266, found 267 $[M + 1]^+$; NMR (200) δ 1.43, 1.70−1.85, 2.2−2.7, 3.2−3.35, 34.7, 3.75−3.85, 4.0−4.15, 5.7−5.9, 9.8; ^{13}C NMR 16.2, 21.0, 25.7, 30.8, 39.4, 39.9, 42.9, 45.7, 71.8, 128.6, 136.2, 170.2, 170.9, 171.3, 201.0. Anal. Calcd for $C_{14}H_{18}O_5$ (266.3): C, 63.2; H, 6.8; O, 30.0. Found: C, 63.1; H, 6.7; O, 30.1.

6-Acetoxy-3-methyl-2a,3,5a,6,7,8,8a,8b-octahydro-2-oxo-2*H*-naphtho[1,8-*bc*]furan-8b-carboxylic Acid (4b). A solution of the aldehyde **3a** (500 mg, 1.7 mmol) in THF (5 mL) was added to a suspension of potassium hydride (140 mg, 3.5 mmol) in absolute THF (5 mL). After being stirred at rt for 2 days, the reaction mixture was poured on a mixture of ice and 20 mL of a 2 N HCl solution under an atmosphere of argon. The acidic solution was extracted with CH_2Cl_2, washed with water, and dried over Na_2SO_4. The solvent was evaporated. Ether was added to give the crystalline product (320 mg): yield 64%; mp 192−194 °C; *m*/*z* calcd for $C_{15}H_{18}O_6$ 294.3045, not observed, calcd for $C_{13}H_{16}O_5$ 252.0998, found 252.0995 $[M - C_2H_2O]^+$, calcd for $C_{13}H_{14}O_4$ 234.0892, found 234.1023 $[M - C_2H_4O_2]^+$; NMR (360) δ 1.22 (d, J = 7.5 Hz), 1.45−1.6, 2.10, 2.0−2.2, 2.7−2.8, 3.20 (d, J = 11.5 Hz), 3.35−3.4, 4.39−4.44 (dd, J_1 = 5.3 Hz, J_2 = 11.2 Hz), 5.3−5.4, 5.75−5.81, 5.85−5.90, 9.7−10.1; NMR (360) (pyridine-d_5) δ 1.29, 1.5−1.65, 1.95−2.15, 2.05, 2.2−2.35, 2.65−2.8, 3.50 (d, J = 11.4 Hz, HC^{2a}), 3.7−3.8, 4.5−4.6, 5.75−5.8, 5.9−6.0 (m, HC^6) 6.0−6.05 (dt, HC^5); ^{13}C NMR 19.9, 21.1, 23.4, 26.3, 26.4, 37.2, 47.5, 53.6, 70.4, 78.7, 121.8, 133.0, 170.4, 176.0, 176.2; IR 1705, 1735, 1780, 2700−3600 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_6$ (294.3): C, 61.2; H, 6.1. Found: C, 61.2; H, 6.1.

6-Acetoxy-3-methyl-2a,3,5a,6,7,8,8a,8b-octahydro-2-oxo-2*H*-naphtho[1,8-*bc*]furan-8b-carboxylic Acid Methyl Ester (Methyl Ester of 4b). A sample of the acid **4b** was treated with diazomethane: *m*/*z* calcd for $C_{16}H_{20}O_6$ 308, found 308 $[M]^+$; NMR (60) δ 1.23, 1.4−2.2, 2.13, 2.5−2.9, 3.1, 3.3−3.5, 3.84, 4.3−4.6, 5.1−5.4, 5.4−6.0.

6-Methoxy-3-methyl-2a,3,5a,6,7,8,8a,8b-octahydro-2-oxo-2*H*-naphtho[1,8-*bc*]furan-8b-carboxylic Acid (4d). A solution of the aldehyde **3d** (240 mg, 0.9 mmol) in THF (15 mL) was added to the suspension of potassium hydride (200 mg, 5 mmol) in absolute THF (10 mL). The mixture was stirred at rt for 3 days. Then, under an atmosphere of argon, it was poured on a mixture of ice and 20 mL of a 2 N HCl solution. The cold acidic solution was extracted with ether, washed with water (2×), and dried over Na_2SO_4. The solvent was evaporated. The crude product was filtered through a short column of silica gel. The solution was evaporated, and the residue was crystallized from ether/hexane to give pure product (163 mg): yield 68%; mp 151−152 °C; *m*/*z* calcd for $C_{14}H_{18}O_5$ 266, found 267 $[M + 1]^+$; NMR (200) δ 1.23, 1.30−1.50, 1.85−2.20, 2.65−2.85, 3.20, 3.35−3.45, 3.44, 3.65−3.80, 4.35−4.45, 5.70−5.95. Anal. Calcd for $C_{14}H_{18}O_5$ (266.30): C, 63.15; H, 6.8; O, 30.0. Found: C, 62.8; H, 6.7; O, 29.9.

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Supporting Information Available: ^1H NMR spectra of compounds **1b**−**d**, **2b**−**d**, **3b**−**d**, **4b**, and **4d** and ROESY and decoupling spectra of compound **4b** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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