Controlling the Stereochemistry of the Ring Junction in Hexahydrodibenzofurans

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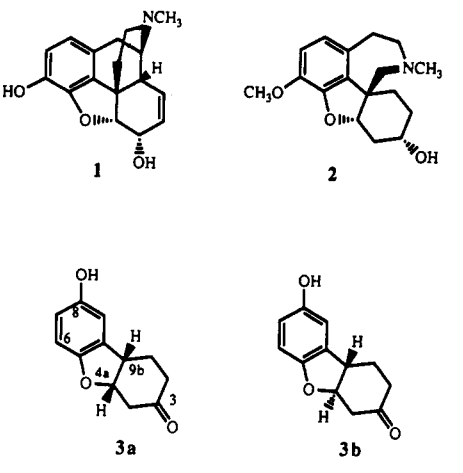
The 8-hydroxy-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-one formed during the acid-catalyzed rearrangement of 1,4,4a,8a-tetrahydro-1-methoxy-1,4-ethanonaphthalene-5,8-dione is, contrary to published reports, exclusively the cis isomer by X-ray crystallography. The stereochemical outcome of this intramolecular Michael addition results from the cyclid nature of the α,β-unsaturated carbonyl, since, in acyclic systems, the addition product is a trans-2,3-disubstituted 2,3-dihydrobenzofuran. The trans relationship of the 2- and 3-substituents in the acyclic system was confirmed by annulation to the *trans*-8-hydroxy-1,2,3,4,4a,9b-hexahydrodibenzofuran-3-one and X-ray crystallographic analysis of the 3-cyanohydrin.

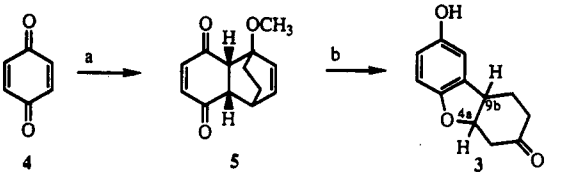
Tetra- and hexahydrodibenzofurans are a common structural feature of alkaloids such as morphine[1] (1) and lycoramine[2] (2) (see Chart I). Methods leading to these ring systems have been and remain one of the challenges of organic synthesis, and interest in developing new methods has intensified due to the varied and potent bioactivities reported for both naturally occurring and synthetic dibenzofurans. Analogues containing the *cis*-tetra- and hexahydrodibenzofuran nucleus have been studied for their analgesic,[3] antidepressant,[4] bronchodilation,[5] antitussive,[6] and CNS stimulant activities[7] and have been used as probes for narcotic receptors.[8]

Our medicinal studies of the bioactivities of this class of compounds required access to hexahydrodibenzofurans with general structures **3a** and **3b**. Hexahydrodibenzofurans have been prepared by a variety of methods, including intramolecular epoxide opening[3] or tosylate displacement[9] by phenoxide ion, palladium-mediated ring closure of the corresponding allyl phenol,[10] Claisen rearrangement of cyclic allyl phenyl ethers,[11] nucleophilic attack of a cyclic enamine on benzoquinone,[12] heteroatom-directed photoarylation,[13] acid rearrangement of tetra-

Chart I

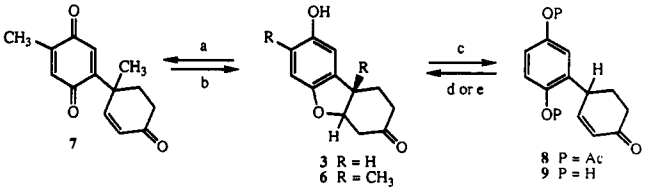


Scheme I[a]



[a] Key: (a) 1-methoxycyclohexa-1,3-diene, benzene, reflux, 4 h; (b) HCl–ethanol–water.

Scheme II[a]



[a] Key: (a) $Fe(NO_2)_3$; (b) H_2, Pd/C; (c) acetic anhydride/NaOAc, reflux; (d) HCl–ethanol–water; (e) piperidine–methanol.

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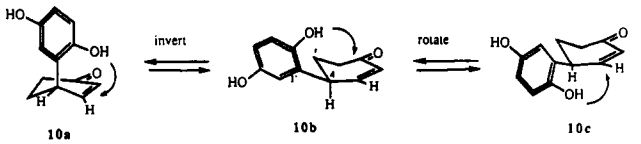
Scheme III



hydronaphthalenediones,[14-17] and hydrogenation of the tetrahydrodibenzofuran.[18] Our specific requirements for an unusual substitution pattern, that is, a hydroxy substituent at the C8 and no substituent at C6, limited the applicability of many literature dibenzofuran syntheses to our purposes.

A particularly direct and convenient synthesis of functionalized hexahydrodibenzofurans is the acid-mediated rearrangement of tetrahydronaphthalene- or -anthracenediones, which in turn are obtained from Diels–Alder addition of 1-methoxy-1,3-cyclohexadienes with appropriate benzo- or naphthoquinones (Scheme I).[14-16] However, the stereochemistry of the 5,6-ring junction formed during this rearrangement has not been unambiguously established. Originally it had been assigned trans (on the basis of an ^1H NMR coupling contant of 9.5 Hz for H4a–H9b),[16] but in another instance it has been designated cis with no evidence cited for that assignment.[17] Our investigation into the chemical and spectral properties of **3** was initiated to establish the stereochemistry of the ring junction and to evaluate the utility of such products in our program.

Results and Discussion

It had previously been reported that oxidation of **6** with ferric nitrate was accompanied by β-elimination to yield quinone **7**, which reclosed to the same isomer of **6** upon reduction (see Scheme II).[14] We found that the β-elimination of **3** can also be effected with sodium acetate in the presence of acetic anhydride, which traps the ring-opened product as the diacetate **8**. Acidic or basic hydrolysis of **8** regenerates **3**, identical with the original material. These results are consistent with observations made during base-catalyzed alkylation attempts.[14]

Models indicate that the β-elimination should be much easier from several conformations of cis-fused **3a** than from those of trans-fused **3b** in which the oxygen is pseudoaxial with poor orientation for elimination. Dreiding models of the trans-fused product indicate a very strained system unlikely to form readily in the Michael ring-closure step. Theoretical arguments also support these model studies: empirical energy calculations suggest that **3b** is at least 3 kcal/mol higher in energy than either the chair or boat conformations of **3a** and that conformations of the precursor **10** that lead to **3b** are at least 2.5 kcal/mol higher in energy than those leading to **3a** (Scheme III).

To confirm these speculations, we obtained an X-ray crystal structure of **3**, which clearly showed that the geometry was *cis*-**3a** (Figure 1). In the crystal lattice the cyclohexanone ring assumes a twist-boat conformation, and there is hydrogen bonding between the phenolic hydroxy group and the carbonyl oxygen of an adjacent molecule.

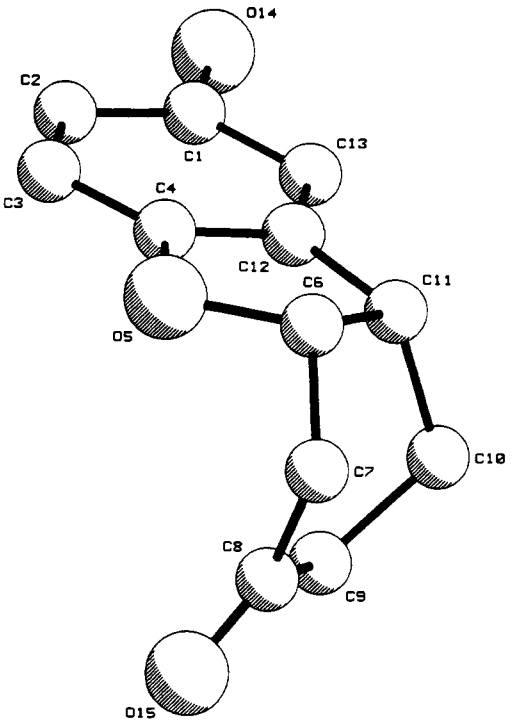
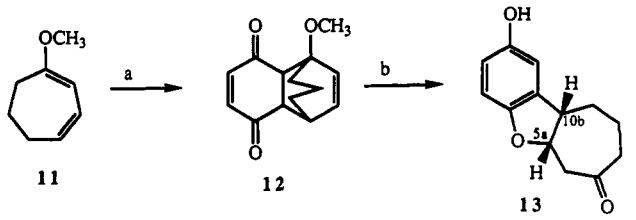


Figure 1. Perspective drawing of the crystal structure of **3a**. Hydrogens have been omitted for clarity.

Scheme IV[a]



[a] Key: (a) benzoquinone; (b) HCl–ethanol–water.

The 9.5-Hz coupling constant for H4a–H9b in solution (CD_3CN) is slightly larger than that expected (8 Hz) for the 19° torsion angle observed for (H4a–C4a–C9b–H9b) in the X-ray structure but not inconsistent with that expected for syn protons in a boat conformation.

This preference for cis ring fusion was maintained also in formation of the analogous 5,7-ring system. Rearrangement of **12** (prepared in a Diels–Alder condensation of **11**[19] with benzoquinone, Scheme IV) afforded a single geometric isomer **13** with an NMR spectrum consistent with cis 5,7 ring fusion ($J_{H5a-H10b}$ = 9 Hz).

Subsequent reactions on the cis-fused system **3a** proceeded with facial selectivity. Thus, reduction of **3a** ($NaBH_4$, EtOAc) proceeded via attack at the less hindered face in the twist-boat conformation to afford the α-OH **14**, as confirmed by X-ray analysis. The X-ray crystal structure of **14** indicated that the cyclohexane ring had adopted a chair conformation with an equatorial hydroxy group. The solution NMR of **14** (CD_3CN) supported the chair conformation, with H4a equatorial and H3 and H9b axial, with $J_{H4a-H9b}$ of 6.5 Hz, as expected for an axial–equatorial relationship. Phenylmagnesium chloride added to **3a** in similar fashion to afford an 8:1 mixture of alcohols of **16** and **17**, (Scheme V). Analysis of ^1H NMR spectra for **16** and **17**, along with the X-ray structure of **16**, indicates that the cyclohexane ring in both adducts adopts a

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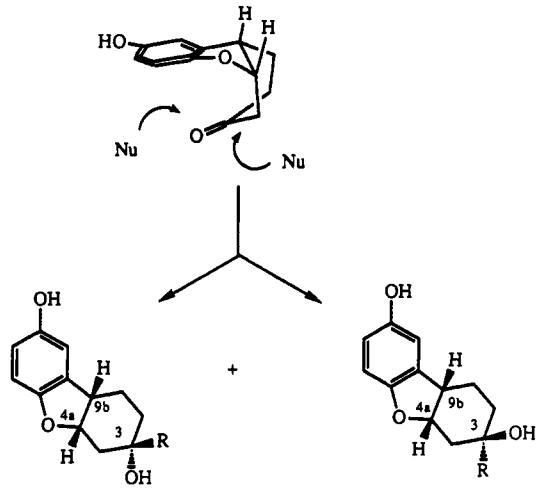
Scheme V

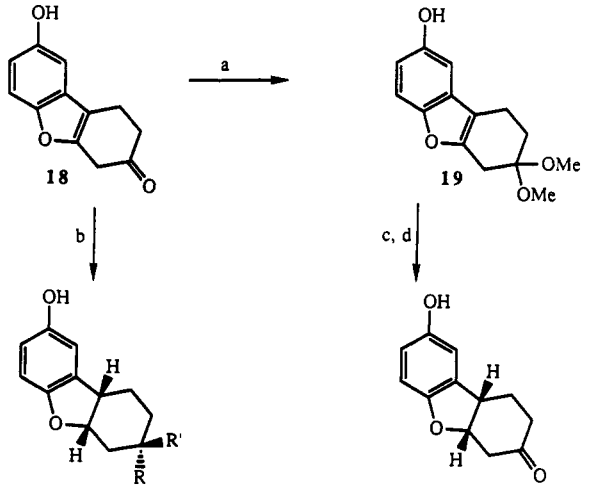


14 R = H
16 R = Ph

15 R = H
17 R = Ph

Reagent	R	Isomer Ratio
$NaBH_4$	H	14:15 = 100:0
Et_3SiH-TFA	H	14:15 = 1:4
PhMgCl	Ph	16:17 = 8:1

Scheme VI[a]



14 R = OH, R' = H
15 R = H, R' = OH

14:15 = 4:1

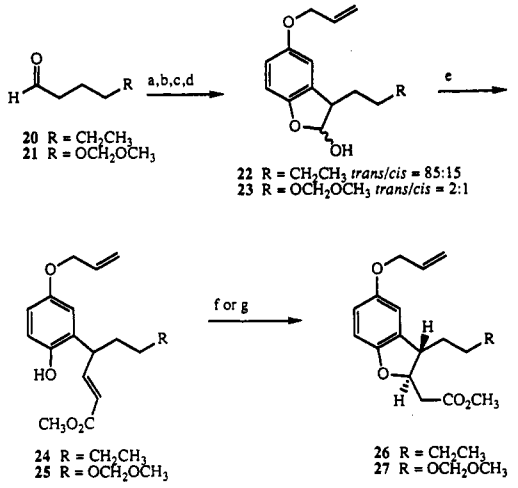
3a

[a] Key: (a) $(CH_3)_2C(OCH_3)_2$, TsOH; (b) Et_3SiH, TFA; (c) Na, liquid NH_3; (d) HCl, H_2O.

chair conformation with the phenyl substituent in an equatorial orientation. X-ray crystallographic studies on the major adduct **16** confirmed the stereochemical assignment at C3. On the other hand, reduction of **3a** with Et_3SiH in trifluoroacetic acid afforded a 4:1 mixture of C3 alcohols, with the β-OH **15** as the predominant isomer.[20] The cyclohexane ring of **15**, as determined by ^1H NMR, is in a chair conformation with H9b equatorial and H3 and H4a axial ($J_{H4a-H9b}$ = 6.5 Hz).

The fused-ring system directed the stereochemical outcome during reduction of the tetrahydro analogue **18**

Scheme VII[a]



20 R = CH_2CH_3
21 R = OCH_2OCH_3

22 R = CH_2CH_3 *trans/cis* = 85:15
23 R = OCH_2OCH_3 *trans/cis* = 2:1

24 R = CH_2CH_3
25 R = OCH_2OCH_3

26 R = CH_2CH_3
27 R = OCH_2OCH_3

[a] Key: (a) piperidine, *p*-TsOH, benzene, reflux; (b) benzoquinone; (c) KO-*t*-Bu, allyl bromide, THF; (d) H_2O, silica gel; (e) $Ph_3PCHCO_2CH_3$; THF; (f) piperidine, methanol, reflux; (g) 2 months, neat, room temperature.

(Scheme VI).[14] Sodium metal reduction of **19** proceeded stereospecifically to the thermodynamically more stable cis isomer **3a** as expected from empirical energy calculations. Hydrogenation of **18** with triethylsilane–trifluoroacetic acid, conditions that normally produce mixtures of trans and cis isomers from the reduction of acyclic 2,3-disubstituted heterocycles,[18] afforded a 4:1 mixture of cis isomers **14** and **15** as the only products.

On the basis of these findings, it was of interest to determine whether the trans isomer could in fact be prepared. Three factors seemed important: the trans geometry would have to be established before the six-membered ring was formed; a carbonyl group could not be used at what would become C1 or C4 of **3b** since (1) such analogues might be expected to epimerize to the cis isomer and (2) dihydrobenzofurans of this type often spontaneously dehydrogenate to benzofurans;[21] and finally the eventual carbonyl group at C3 would have to be replaced by latent functionality to be unmasked in the last step in the absence of acid or base. The intramolecular alkylation of a cyanohydrin would satisfy the above criteria, and such transformations are well precedented in natural product synthesis.[22] The key step would then be preparation of the trans-2,3-disubstituted 2,3-dihydrobenzofuran.

The rapid and reversible intramolecular β-elimination–1,4-addition observed with **3a** should occur with acyclic analogues as well; that is, under basic, protic conditions the phenolic OH of acrylate **24** should add to the α,β-unsaturated ester to afford the thermodynamically more stable trans isomer (as expected based on empirical energy calculations). The model acrylate **24** was prepared in a three-step sequence. Conjugate addition of the enamine of **20** to benzoquinone followed by in situ alkylation with allyl bromide and hydrolysis afforded lactol **22**,[23] which condensed with methyl (triphenylphosphoranylidene)-

(20) Mechanistic studies of the stereochemistry of acid-catalyzed reduction of ketones by silanes have been described by the following: Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3829–3834. Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3835–3838. Doyle, M. P.; McOsker, C. C.; Ball, N.; West, C. T. *J. Org. Chem.* **1977**, *42*, 1922–1928.

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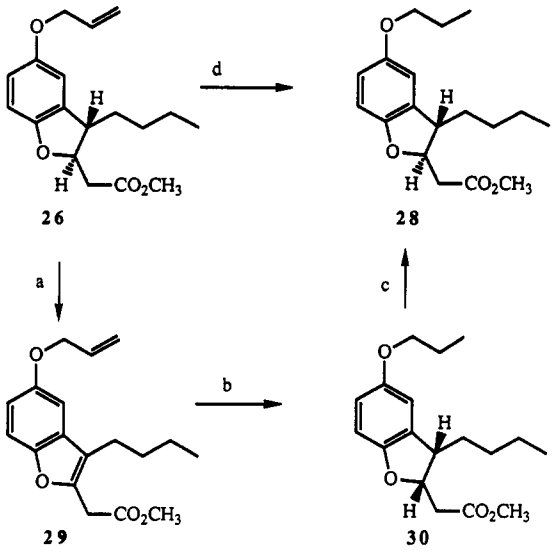
(23) Experimental procedures and spectral data for preparation of this compound are available in the supplementary material.

Scheme VIII[a]



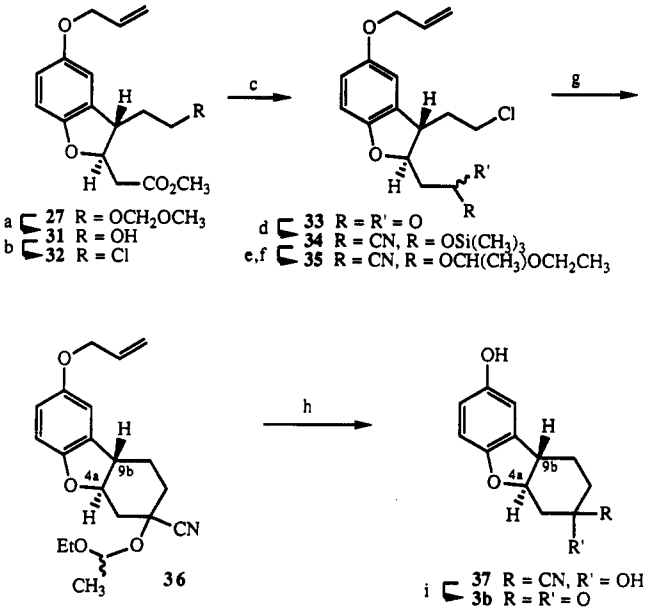
[a] Key: (a) DDQ, benzene, reflux, 15 min; (b) 3 atm of H_2, 10% Pd/C, CH_3OH, 24 h; (c) catalytic piperidine, methanol, reflux, 30 min; (d) 3 atm of H_2, 10% Pd/C, EtOAc, 15 min.

acetate to form (*E*)-acrylate **24**.[23] Treatment with piperidine converted **24** to a single 2,3-dihydrobenzofuran **26** (Scheme VII)[23] whose ^1H NMR spectrum revealed a J_{H2-H3} of 5 Hz, which is consistent with its expected trans ring stereochemistry.[24]

Additional support for the trans assignment was obtained by the following sequence. Hydrogenation of **26** afforded the propyl ether **28**[23] with retention of the C2 and C3 stereochemistry (J_{H2-H3} = 5 Hz, Scheme VIII). Additionally, **26** was oxidized to the benzofuran **29**[23] with DDQ and reduced catalytically (H_2, Pd/C) to afford a new dihydrobenzofuran **30**[23] whose ^1H NMR shows a downfield shift of 0.5 ppm for H2 and H3 relative to the corresponding protons of **28**. The 7.5-Hz coupling constant for H2–H3 in **30** is consistent with that expected for the cis isomer.[24] That **28** was indeed the thermodynamic product was confirmed by isomerization of **30** to **28** upon heating with catalytic piperidine in methanol.

The preparation of **3b** required a potential leaving group on the β-carbon of the 3-substituent. Conjugate addition of the enamine of **21**[25] to benzoquinone, alkylation, and hydrolysis afforded the lactol **23** in 64% yield. Reaction of **23** with methyl (triphenylphosphoranylidene)acetate afforded (*E*)-acrylate **25**, which cyclized under equilibrating conditions to **27**. About 3% of the cis isomer could be detected by ^1H NMR. Treatment of this mixture with BF_3 in methanol afforded hydroxy ester **31**, which was converted to the corresponding chloride **32** with Lee's reagent (PPh_3–CCl_4 Scheme IX).[26] Selective reduction of **32** with DIBAL-H (−78 °C, toluene) afforded the unstable aldehyde **33** that was immediately converted to **34** with cyanotrimethylsilane.[27] The silyl ether of **34** decomposed under the basic conditions needed to effect ring closure and so was converted to the more stable 1-ethoxyethyl ether **35** by treatment with ethyl vinyl ether and trifluoroacetic acid.

Scheme IX[a]



[a] Key: (a) BF_3, CH_3OH; (b) PPh_3, CCl_4, CH_3CN; (c) DIBAL-H, toluene, −78 °C; (d) $(CH_3)_3SiCN$, KCN, 25 °C; (e) Bu_4NF, CF_3CO-OH, THF, 0 °C; (f) $CH_2CHOCH_2CH_3$, CF_3COOH, THF, 0 °C; (g) $NaN(Si(CH_3)_2$, THF, 60 °C; (h) 10% Pd/C, *p*-TsOH, CH_3OH–C_6-H_6, 70 °C; (i) $(CH_3)_2SO$, 45 °C, 100-mm vacuum.

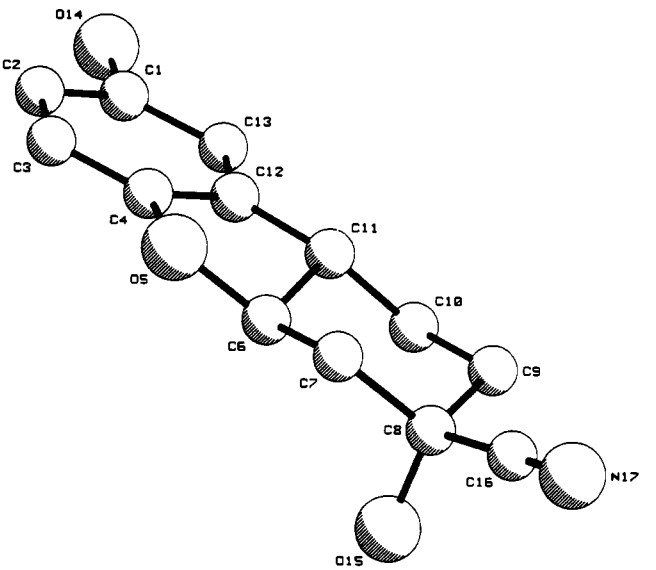


Figure 2. Perspective drawing of the crystal structure of **37**. Hydrogens have been omitted for clarity.

Compound **35** was obtained as a mixture of three diastereometers that were not separated at this time.

Reaction of **35** with sodium hexamethyldisilazide in THF at 60 °C afforded a mixture of diastereomers whose structures were tentatively assigned as **36**. Spectroscopic (^1H NMR) examination of this material indicated that the methine absorbances of the dihydrobenzofuran had shifted about 0.5 ppm upfield and now showed a 12-Hz coupling expected for the trans-diaxial orientation. Deprotection (10% Pd/C, benzene–methanol, catalyst TsOH, reflux)[28] afforded a crystalline cyanohydrin **37**, whose structure was verified by X-ray crystallographic analysis (Figure 2). The

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(28) Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558–559. Carless, H. A. J.; Haywood, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 980–981.

Table I. Conformational Energy of Hexahydrodibenzofuran Analogues

compound	rel energy (kcal/mol)	compound	rel energy (kcal/mol)
3a (twist-boat)	0	**3b** (chair)	4.47
3a (chair, O5 ax)	2.01	**3b** (twist-boat)	7.19
3a (chair, O5 eq)	2.16		

Table II. Conformational Energy of Dihydrobenzofuran Analogues

compound	rel energy (kcal/mol)	compound	rel energy (kcal/mol)
26 (trans)	0	**27** (trans)	0
26 (cis)	3.41	**27** (cis)	5.62

cyanohydrin adduct was converted to ketone **3b** in 63% yield by heating a solution of **37** in DMSO under vacuum at 45 °C. As expected, a large 12.5-Hz coupling between H4a and H9b was observed in the ^{1}H NMR spectrum of **3b**.

In summary, the product formed in the acid-catalyzed rearrangement of 1,4,4a,8a-tetrahydro-1-methoxy-1,4-ethanonaphthalene-5,8-dione (**5**) has been established as *cis*-1,2,3,4,4a,9b-hexahydro-8-hydroxydibenzofuran-3-one (**3a**). This structural assignment is based on X-ray crystallographic analysis and spectroscopic comparison with the authentic trans isomer. The same *cis*-hexahydrodibenzofuran is formed during deacylation of **8** and cyclization under either acidic or basic conditions. The stereochemical outcome of this intramolecular Michael addition of hydroquinone to an α,β-unsaturated carbonyl is controlled by the nature of the α,β-unsaturated carbonyl. In cyclic systems, the product is the *cis*-hexahydrodibenzofuran while in acyclic systems the product is a *trans*-2,3-disubstituted 2,3-dihydrobenzofuran. A *trans*-dihydrobenzofuran prepared in this manner has been elaborated to the *trans*-hexahydrodibenzofuran without affecting the stereochemistry of the fused-ring system.

Experimental Section

Melting points are uncorrected. NMR spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet, p, pentuplet; m, multiplet; comp, complex; AB, AB pattern; and b, broad. Where necessary, peak assignments were determined by decoupling, and higher order couplings were confirmed with Varian simulation software. Mass spectra were measured with xenon 8-keV fast atom bombardment (FAB) in a dithiothreitol matrix or electron impact at 70 eV.

Unless otherwise indicated, reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Reagent grade triethylamine, dichloromethane, benzene, toluene, hexane, and dimethyl sulfoxide were stored under nitrogen over 4A sieves. Reactions were routinely conducted in oven-dried (125 °C) or flame-dried glassware under nitrogen atmosphere.

Analytical thin-layer chromatography (TLC) was performed with 2.5 cm × 10 cm plates coated with a 0.25-mm thickness of silica gel containing PF-254 indicator. Compounds were visualized by UV, ceric sulfate/H_2SO_4 charring, or iodine vapor. Flash chromatography was conducted according to the procedures developed by Still[29] with the solvents indicated.

Empirical energy calculations (molecular mechanics) were obtained with the MM2X force field (Merck's extended MM2[30]) with the program OPTIMOL. Individual conformations were found by full geometry optimization starting with appropriate conformations (Table I and II). Torsional profiles were obtained from a series of constrained optimizations about the (C4–C1′) bond of **10b** at 10° intervals for a range of 360°.

Crystals for X-ray diffraction studies were formed from ethyl acetate–hexane, and reflections were measured with an automatic four-circle diffractometer equipped with Cu radiation. Structures were solved with a direct-methods approach and difference Fourier analyses and refined with full-matrix least-squares techniques.[31]

(4a*S,9b*S**)-1,2,3,4,4a,9b-Hexahydro-8-hydroxydibenzofuran-3-one (3a).** In a modification of the literature procedure,[14] a solution of 6.22 g (30 mmol) of 1,4,4a,8a-tetrahydro-1-methoxy-1,4-ethanonaphthalene-5,8-dione[14] in 100 mL of ethanol and 2 mL of 1.0 M HCl was stirred at room temperature for 18 h. The solution was concentrated in vacuo, and the residue was partitioned between ethyl acetate and saturated NaCl solution. The ethyl acetate layer was washed twice with saturated NaCl solution, and the aqueous extracts were back-extracted sequentially with an equal portion of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated to an oil that crystallized from ethyl acetate–hexane to afford 4.95 g (81%) of colorless prisms: mp 142–145 °C (lit.[14] mp 143–145 °C); IR (KBr) 3300, 2960, 2890, 1710, 1510 (s), 1480, 1405, 1365, 1325, 1300, 1280, 1245, 1200, 1150, 1020, 950, 910, 870, 825, 780 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.8–2.0 (m, 2 H), 2.1–2.3 (m, 2 H), 2.66 (AB, dd, J = 16.5, 4.0 Hz, 1 H), 2.81 (AB, dd, J = 16.5, 4.0 Hz, 1 H), 3.71 (m, 1 H), 5.18 (dt, J = 9.5, 4.0 Hz, 1 H), 6.49 (s, b, 1 H), 6.54 (m, 2 H), 6.71 (m, 1 H); mass spectrum, m/e 205 (FAB, M + H, 100). Anal.: C, H.

4-[2,5-Bis(acetyloxy)phenyl]-2-cyclohexenone (8). A mixture of 1.02 g (5.0 mmol) of **3a** and 0.420 g (5.0 mmol) of sodium acetate in 10 mL of acetic anhydride was heated at reflux for 15 min. The solution was concentrated in vacuo, and the residue was partitioned between ether and water. The aqueous layer was washed with two portions of ether, and the organic exctracts were washed sequentially with saturated $NaHCO_3$ solution and then saturated NaCl solution, combined, and dried ($MgSO_4$). The solution was concentrated and the residue crystallized from ether–hexane to afford 1.14 g (79%) of colorless needles: mp 87–88 °C; IR (KBr) 3040, 2940, 2860, 1745, 1670, 1490, 1420, 1370, 1200, 1130, 1090, 1050, 1015, 925, 900, 880, 825, 780 cm^{-1}; NMR (200 MHz, CD_3CN) δ 1.9–2.1 (m, 2 H), 2.25 (s, 3 H), 2.28 (s, 3 H), 2.4–2.5 (m, 2 H), 3.19 (dddd, J = 10, 5, 3, 2.5 Hz, 1 H), 6.08 (dd, J = 10.5, 3, 1 Hz, 1 H), 6.88 (ddd, J = 10.5, 2.5, 1.5 Hz, 1 H), 7.0–7.2 (m, 3 H); FAB mass spectrum, m/e 288 (44, M$^+$).

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(30) The MM2X force field is derived in large part from the MM2 force field.[32] For intramolecular interactions, the force field includes all the type of interactions that are in MM2, and functional form of interaction is identical with that in MM2 with one exception. The electrostatic term is represented by Coulomb's law acting on atom-centered point charges. These atomic charges q are, however, derived from bond dipole moments $q = 1/4.803 \sum_i \mu_i r_{i0}$, where μ is the bond dipole moment, r_0 is the reference bond length, and the sum extends over all the bonds for a given atom. The parameters used by MM2X for the molecules studied along with their MM2 counterparts[32] are given in Tables III–VI in the supplementary material. MM2X does not use lone pairs on aliphatic amines, alcohol, and ether oxygens, and carboxylic acid and ester oxygens and the parameter differences are due primarily to the need to make up for the elimination of lone pairs on oxygen, reproduction of gas-phase dimerization energies of acids and amides, and incorporation of parameters for aromatic carbon based on the AMBER force field.[33] Parameters for the nonbonded, out-of-plane, and stretch–bend interactions are taken directly from MM2 without change.

(31) The following library of crystallographic programs was used. SHELXS-86: G. M. Sheldrick, University of Gottingen, Gottingen, West Germany, 1986. PLUTO: W. D. S. Motherwell and W. Clegg, University of Cambridge, Cambridge, England, 1978. SDP PLUS V1.1: Y. Okaya and B. A. Frenz, B. A. Frenz and Associates, College Station, TX, 1984.

(32) Allinger, N. L.; Yuh, Y. H. *QCPE* **1981**, *13*, 395. There are slight differences between the parameters found in this program and those reported in the original reference to MM2.[34] In addition, two modifications designed for C_{ar}–C_{ar} bonds are also used: r_0 = 1.3937 Å and k_r = 8.0667 mdyn Å^{-1}).

(33) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S., Jr.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765–784.

(34) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134.

Conversion of 8 to 3a. Method A (Acidic Conditions). A solution of 0.288 g (1.0 mmol) of 8 in 5 mL of methanol and 0.1 mL of 1.0 M HCl was stirred at room temperature for 18 h. The solution was concentrated and the residue dissolved in ethyl acetate, dried ($MgSO_4$), and concentrated to a yellow oil that crystallized from ethyl acetate–hexane to afford 0.143 g of colorless needles (70%), mp 142–143 °C, not depressed by admixture with authentic 3a.

Method B (Basic Conditions). A solution of 0.288 g (1.0 mmol) of 8 in 10 mL of methanol and 0.5 mL of piperidine was heated at reflux for 4 h. The solution was concentrated and the residue dissolved in ethyl acetate, dried ($MgSO_4$), and concentrated to a yellow oil that crystallized from ethyl acetate–hexane to afford 0.159 g of colorless needles (78%), identical with 3a prepared above by mp (141–143 °C) and spectral comparisons.

1,4,4a,8a-Tetrahydro-1-methoxy-1,4-propanonaphthalene-5,8-dione (12). A solution of 0.500 g (4.63 mmol) of benzoquinone and 2.50 g (20 mmol) of 1-methoxy-1,3-cycloheptadiene[19] in 20 ml of toluene was heated at reflux for 24 h. The solution was concentrated in vacuo and the residue purified by flash chromatography (3-cm column) with 10% ethyl acetate–hexane to afford 0.886 g (81%) of pale yellow solid that was a mixture of exo and endo adducts: mp 72–74 °C; IR (KBr) 3120, 2960, 2840, 1740, 1720, 1660, 1595, 1460, 1440, 1370, 1260, 1240, 1185, 1090, 990, 850, 810, 715 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.40–2.10 (m, 6 H), 2.95 (dd, J = 4.0, 2.0 Hz, 1 H), 3.04 (s b, 0.7 H), 3.08 (s, 0.6 H), 3.31 (s, 2.4 H), 3.51 (s b, 0.2 H), 6.19 (m, 2 H), 6.63 (m, 2 H); FAB mass spectrum, m/e 232 (56, M^+), 202 (100).

(5a*S,10b*S**)-1*H*-2,3,4,5,5a,10b-Hexahydro-9-hydroxybenzo[*b*]cyclohepta[*d*]furan-4-one (13).** A sample of 0.232 g (1.00 mmol) of 12 was dissolved in 5 mL of ethanol and 0.5 mL of 1 M HCl. The solution was stirred at room temperature for 1 h and then concentrated, and the residue was crystallized from ethyl acetate–hexane to afford 0.178 g 9, 4 of colorless needles: mp 190 °C dec; IR (KBr) 3380, 2960, 2860, 1685, 1600, 1480, 1360, 1350, 1290, 1260, 1205, 1195, 1130, 1035, 1010, 980, 810, 770 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.64 (m, 1 H), 1.92 (m, 1 H), 2.06 (m, 1 H), 2.41 (AB, dt, J = 13, 7 Hz, 1 H), 2.45 (AB, dt, J = 13, 7 Hz, 1 H), 2.83 (AB, dd, J = 13, 4 Hz, 1 H), 2.94 (AB, dt, J = 13, 9 Hz, 1 H), 3.54 (dt, J = 9, 4 Hz, 1 H), 4.92 (dt, J = 9, 4 Hz), 6.44 (s b, 1 H), 6.54 (m, 2 H), 6.65 (m, 1 H); mass spectrum, m/e 218 (91), 147 (100), 136 (55), 123 (36), 105 (24), 91 (44), 77 (38), 65 (34), 55 (56). Anal.: C, H.

(4a*S,9b*S**,3*S**)-1,2,3,4,4a,9b-Hexahydrodibenzofuran-3,8-diol (14).** A solution of 0.204 g (1.0 mmol) of 3a in 10 mL of ethyl acetate was cooled to 0 °C in an ice bath. To this was added 0.035 g (1.0 mmol) of $NaBH_4$, and the solution was stirred at 0 °C for 4 h. Excess hydride was decomposed by addition of 1 mL of saturated NH_4Cl solution, and the mixture was partitioned between ethyl acetate and 0.02 M HCl. The aqueous layer was washed with two portions of ethyl acetate, and the organic extracts were washed sequentially with saturated NaCl solution, combined, and dried ($MgSO_4$). The solution was filtered and concentrated, and the residue was crystallized from ethyl acetate–hexane to afford 0.198 g (96%) of colorless prisms: mp 147–148 °C; IR (KBr) 3350 (b), 3150 (b), 2960, 2890, 1605, 1480, 1360, 1280, 1260, 1210, 1190, 1135, 1095, 1060, 960, 900, 870, 800, 760 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.25 (m, 1 H), 1.42 (ddd, J = 13, 9, 8.5 Hz, 1 H), 1.70 (m, 2 H), 2.06 (m, 2 H), 2.69 (d, J = 5.5 Hz, 1 H, –OH), 3.30 (dt, J = 6.5, 5 Hz, 1 H), 3.57 (ddt, J = 9, 5.5, 4.5 Hz), 4.74 (ddt, J = 8.5, 6.5 Hz, 1 H), 6.47 (s b, 1 H), 6.52 (AB, ddd, J = 8.5, 2.5, 1 Hz, 1 H), 6.56 (AB, dd, J = 8.5, 0.5 Hz, 1 H), 6.64 (ddd, J = 2.5, 1, 0.5 Hz, 1 H); mass spectrum, m/e 206 (30, M^+), 149 (18), 147 (28), 123 (32), 91 (24), 77 (40), 73 (100), 69 (24), 57 (20). Anal.: C, H.

(4a*S,9b*S**,3*R**)-1,2,3,4,4a,9b-Hexahydrodibenzofuran-3,8-diol (15).** A solution of 0.204 g (1.0 mmol) of 3a in 2 mL of trifluoroacetic acid was cooled to 0 °C. To this was added 0.5 mL (3.2 mmol) of triethylsilane, and the solution was stirred at 0 °C for 1 h. The solution was concentrated, and the residual trifluoroacetic acid was removed by azeotropic distillation with toluene. The residue was crystallized from ether to afford 0.114 g (56%) of white prisms: mp 176–177 °C; IR (KBr) 3400 (b), 3180 (b), 2940, 2860, 1605, 1475, 1375, 1280, 1260, 1205, 1180, 1135, 1050, 970, 890, 870, 820, 760 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.28 (m, 2 H), 1.64 (AB, ddd, J = 14, 10, 5.5 Hz, 1 H), 2.71 (m, 1 H), 2.23 (AB, dddd, J = 14, 4, 3.5, 2 Hz, 1 H), 2.78 (d, J = 4.5, 1 H, –OH), 2.99 (dt, J = 9, 6.5 Hz, 1 H), 3.74 (dtt, J = 10, 5.5, 4.5 Hz, 1 H), 4.84 (dt, J = 6.5, 4 Hz, 1 H), 6.39 (s b, 1 H), 6.50 (AB, dd, J = 8, 2.1 Hz, 1 H), 6.56 (AB, d, J = 8 Hz, 1 H), 6.60 (d, J = 2.5 Hz, 1 H); FAB mass spectrum, m/e 361 (28, M + matrix), 207 (100, M^+). Anal.: C, H.

(4a*S,9b*S**,3*S**)- and (4a*S**,9b*S**,3*R**)-1,2,3,4,4a,9b-Hexahydro-3-phenyldibenzofuran-3,8-diols (16 and 17).** A solution of 4.08 g (20.0 mmol) of 3a in 50 mL of THF was cooled to –78 °C in a dry ice–acetone bath. Then 30 mL of a 2 M solution of phenylmagnesium chloride in tetrahydrofuran was added dropwise over 15 min, and the mixture was stirred, first at –78 °C for 1 h and then at 0 °C for 30 min. The reaction was quenched by addition of 20 mL of saturated NH_4Cl solution, and the mixture was partitioned between ethyl acetate and saturated NH_4Cl solution. The aqueous layer was washed with ethyl acetate, and the organic extracts were washed sequentially with saturated NH_4Cl and saturated NaCl solution, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (5-cm column) with 25% ethyl acetate–hexane eluant to afford 2.96 g (53%) of colorless needles: mp 162–163 °C; IR (KBr) 3380, 3230, 2940, 2870, 1610, 1490, 1445, 1360, 1260, 1205, 1180, 1140, 1100, 1090, 1060, 980, 945, 845, 820, 760, 700 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.70 (m, 2 H), 1.86 (m, 1 H), 2.10 (m, 1 H), 2.28 (d, J = 3.5 Hz, 2 H), 3.09 (ddd, J = 10, 7, 6 Hz, 1 H), 4.68 (ddt, J = 6, 3.5, 1 Hz, 1 H), 6.46 (s b, 1 H), 6.56 (AB, dd, J = 8.5, 2.5 Hz, 1 H), 6.65 (AB, d, J = 8.5 Hz, 1 H), 6.74 (d, J = 2.5 Hz, 1 H), 7.25 (m, 1 H), 7.36 (m, 2 H), 7.54 (m, 2 H); mass spectrum, m/e 282 (8, M^+), 264 (8), 134 (24), 105 (26), 91 (14), 77 (12), 73 (100), 57 (12). Anal.: C, H.

Later fractions were pooled and concentrated to afford 0.385 g (7%) of the C3 epimer (17): mp 154–155 °C; IR (KBr) 3400, 3160, 2950, 2890, 1600, 1485, 1460, 1350, 1270, 1250, 1180, 1120, 1100, 1060, 970, 920, 900, 870, 830, 760, 700 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.61 (AB, ddd, J = 14.5, 5, 4.5 Hz, 1 H), 1.70 (AB, dd, J = 14, 9.5 Hz, 1 H), 1.77 (AB, ddd, J = 14.5, 12, 4.5 Hz, 1 H), 2.03 (AB, ddd, J = 14, 6.5, 2 Hz, 1 H), 2.17 (AB, ddt, J = 14.5, 8, 4 Hz, 1 H), 2.32 (AB, dddd, J = 14.5, 12, 6.5, 5 Hz, 1 H), 3.59 (ddt, J = 8, 5.5, 1 Hz, 1 H), 5.03 (ddd, J = 10, 8, 6 Hz, 1 H), 6.44 (s b, 1 H), 6.55 (AB, ddd, J = 8.5, 2, 1 Hz, 1 H), 6.57 (AB, dd, J = 8.5, 1 Hz, 1 H), 6.71 (dt, J = 2, 1 Hz, 1 H), 7.19 (m, 1 H), 7.28 (m, 2 H), 7.35 (m, 2 H); mass spectrum, m/e 282 (100, M^+), 164 (58), 160 (64), 147 (52), 133 (54), 123 (38), 105 (86), 91 (32), 81 (38), 77 (48), 73 (62), 69 (66), 57 (34), 55 (42). Anal.: C, H.

(4a*S,9b*S**,3*S**)-1,2,3,4,4a,9b-Hexahydro-3-phenyldibenzofuran-3,8-diol (16).** A solution of 1.02 g (5 mmol) of 3a in 20 mL of THF and 1 mL (7.2 mmol) of triethylamine was cooled to 0 °C in an ice bath, and to this was added 0.72 mL (6 mmol) of chlorotrimethylsilane. The solution was stirred at 0 °C for 30 min, then filtered, and concentrated. The residue was dissolved in 20 mL of THF and cooled to –78 °C in a dry ice–acetone bath. To this was added 10 mL of a 2 M solution of phenylmagnesium chloride in tetrahydrofuran dropwise, and the mixture was stirred, first at –78 °C for 1 h and then at 0 °C for 30 min. The reaction was quenched by addition of 20 mL of saturated NH_4Cl solution, and the mixture was partitioned between ethyl acetate and saturated NH_4Cl solution. The aqueous layer was washed with ethyl acetate, and the organic extracts were washed sequentially with saturated NH_4Cl and saturated NaCl solution, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on a 4-cm column with 25% ethyl acetate–hexane eluant to afford 0.87 g (62%) of colorless needles, identical with the major isomer (16) prepared above by melting point (162–163 °C) and spectral comparisons.

3,3-Dimethoxy-1,2,3,4-tetrahydrodibenzofuran-8-ol (19). A suspension of 2.02 g (10.0 mmol) of 18[14] and 0.050 g (0.250 mmol) *p*-toluenesulfonic acid in 15 mL of 2,2-dimethoxypropane was heated at reflux for 18 h. The solution was allowed to cool to room temperature and was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The aqueous layer was washed with ethyl acetate, and the combined organic extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (4-cm column) with 25% ethyl acetate–hexane and crystallized from ethyl acetate-hexane to afford 1.89 g (76%) of white needles: mp 148–150 °C (lit.[14] mp 138–140 °C); IR (CH_2Cl_2) 3300, 3200, 2960, 2840,

1700 (w), 1620, 1590, 1460, 1390, 1370, 1290, 1250, 1175, 1090, 1060, 995, 960, 890, 860, 840, 790 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.10 (t, J = 6.5 Hz, 2 H), 2.59 (t, J = 6.5 Hz, 2 H), 3.01 (s, 2 H), 3.32 (s, 6 H), 4.68 (s, 1 H), 6.67 (dd, J = 8.5, 2.5 Hz, 1 H), 6.80 (d, J = 2.5 Hz, 1 H), 7.20 (d, J = 2.8 Hz, 1 H); mass spectrum m/e = 248 (FAB, M^+).

Sodium Metal Reduction of 19. A suspension of 0.450 g (2 mmol) of **19** in 30 mL of liquid ammonia was stirred under reflux. To this was added 0.030 g (13 mmol) of sodium metal in small chips, and the solution was stirred under reflux until the blue disappeared. The ammonia was allowed to evaporate, and the residue was dissolved in 0.1 M HCl. The solution was stirred at room temperature for 6 h, and then it was partitioned between ethyl acetate and saturated NaCl solution. The aqueous layer was washed with two portions of ethyl acetate, and the organic extracts were washed sequentially with two portions of saturated NaCl solution, dried ($MgSO_4$), and concentrated. The residue crystallized from ethyl acetate–hexane to afford 0.212 g (52%) of colorless prisms that were identical with compound **3a** by melting point (142–144 °C) and NMR spectral comparisons.

Triethylsilane–TFA Reduction of 18. A solution of 2.02 g (10 mmol) of **18**[14] in 20 mL of trifluoroacetic acid and 5 mL of triethylsilane was stirred at room temperature for 24 h. Then 10 mL of methanol was added, and the solution was stirred for an additional 30 min. The solution was concentrated, and the remaining acid was removed by azeotropic distillation with toluene. The residue was crystallized from ethyl acetate–hexane to afford 1.58 g (77%) of white prisms that represented a 4:1 mixture of diastereomers **14** and **15** by NMR spectral comparisons.

(2*S,3*S**)-2-Hydroxy-3-(3,5-dioxahexyl)-5-(2-propenyloxy)-2,3-dihydrobenzofuran (23).** A solution of 26.4 g (200 mmol) of **21**,[25] 20 mL (18.7 g, 200 mmol) of piperidine, and 0.500 g (2.90 mmol) of *p*-toluenesulfonic acid in 250 mL of benzene was heated at reflux in a 1000-mL flask that had been fitted with a Dean–Stark condenser. After 4 h the solution was cooled and concentrated under reduced pressure. The residue was dissolved in 100 mL of benzene, and the solution was added dropwise to 1000-mL flask containing a rapidly stirring solution of 21.6 g (200 mmol) of freshly sublimed benzoquinone in 200 mL of benzene. The solution grew hot during the addition, and a dark red precipitate formed. After 4 h the solids were dissolved by the addition of 400 mL of dry THF. The solution was cooled to 0 °C in an ice bath, and to the solution were added 44.8 g (400 mmol) of potassium *tert*-butoxide and 22 mL (300 mmol) of allyl bromide. The mixture was stirred for 24 h, until alkylation was complete. The reaction mixture was partitioned between ether and water, and the ether layer was washed and saturated $NaHCO_3$ solution and saturated NaCl solution. The aqueous layers were washed sequentially with ether, and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (12-cm column) with 20% ethyl acetate–hexane to afford 23.6 g (46%) of a pale orange oil. All attempts to distill this product and subsequent intermediates resulted in thermally induced Claisen rearrangement to the *o*-allylphenols. IR (CH_2Cl_2) 3590, 3380 (b), 3050, 2960, 2890, 1750 (w), 1600 (w), 1490, 1420, 1240, 1190, 1150, 1110, 1055, 1000, 930 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.92 (dt, J = 4.5 Hz, 2 H), 3.18 (m, 0.67 H, *trans*-H3), 3.31 (s, 1 H, *cis*-OCH_3), 3.42 (s, 2 H, *trans*-OCH_3), 3.49 (m, 0.33 H, *cis*-H3), 3.57 (t, J = 6.5 Hz, 2 H), 4.44 (dt, J = 5.5, 1.5 Hz, 2 H), 5.31 (dq, J = 10.5, 1.5 Hz, 1 H), 5.37 (dq, J = 17, 1.5 Hz, 1 H), 5.70 (d, J = 2 Hz, 0.67 H, *trans*-H2), 5.89 (d, J = 6 Hz, 0.33 H, *cis*-H2), 6.02 (ddt, J = 17, 10.5, 5.5 Hz, 1 H), 6.71 (m, 2 H), 6.80 (m, 1 H); mass spectrum, m/e 280 (5, M^+), 218 (16), 177 (66), 149 (12), 98 (100), 84 (22), 73 (64), 55 (16). Anal.: C, H.

Methyl 4-[2-Hydroxy-5-(2-propenyloxy)phenyl]-7,9-dioxa-2-decenoate (25). A solution of 0.280 g (1 mmol) of **23** and 0.714 g (2 mmol) of methyl (triphenylphosphoranylidene)acetate in 10 mL of THF was heated at reflux for 4 h (until no starting material remained by TLC). The solution was concentrated, and the residue was taken up in ether and filtered. The filtrate was concentrated and purified by flash chromatography (3-cm column) with 30% ethyl acetate–hexane to afford 0.305 g (91%) of a pale orange oil: IR (CH_2Cl_2) 3380, 3360, 3060, 2960, 2880, 1730, 1655, 1600, 1490, 1435, 1200, 1180, 1160, 1100, 1080, 985, 930 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.02 (m, 1 H), 2.13 (m, 1 H), 3.37 (s, 3 H), 3.43 (m, 1 H), 3.58 (m, 1 H), 3.74 (s, 3 H), 4.00 (dq, J = 7, 1.5 Hz), 4.48 (dt, J = 5.5, 1.5 Hz, 2 H), 4.65 (s, 2 H), 5.31 (dq, J = 11, 1.5 Hz, 1 H), 5.43 (dq, J = 17, 1.5 Hz, 1 -H), 5.93 (dd, J = 15.5, 1.5 Hz, 1 H), 6.03 (ddt, J = 17, 11, 5.5 Hz, 1 H), 6.68 (m, 2 H), 6.79 (m, 1 H), 7.19 (d, J = 15.5 Hz, 1 H); mass spectrum, m/e 336 (62, M^+), 273 (34), 263 (46), 233 (72), 231 (52), 177 (100), 161 (54), 147 (46), 131 (24), 115 (26), 91 (56), 77 (42), 65 (38), 59 (54), 55 (52). Anal.: C, H.

Methyl (2*R,3*S**)-[3-(3,5-Dioxahexyl)-2,3-dihydro-5-(2-propenyloxy)-2-benzofuranyl]acetate (27).** A solution of 0.672 g (2 mmol) of **25** and 0.1 mL of piperidine in 10 mL of methanol was heated at reflux. After 1 h, cyclization was complete by TLC (25% ethyl acetate–hexane), and the solution was concentrated under vacuum and purified by flash chromatography (3-cm column) with 25% ethyl acetate–hexane to afford 0.520 g (77%) of a pale orange oil: IR (CH_2Cl_2) 3060, 2990, 2970, 2880, 2745, 1630, 1490, 1430, 1250, 1200, 1180, 1155, 1115, 1080, 1000, 930 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.96 (dt, J = 6.5, 3.5 Hz, 1 H), 1.99 (dt, J = 6.5, 2 Hz, 1 H), 2.66 (AB, dd, J = 16, 5.5 Hz, 1 H), 2.75 (AB, dd, J = 16, 8 Hz, 1 H), 3.23 (dt, J = 7, 5.5 Hz, 1 H), 3.38 (s, 3 H), 3.69 (t, J = 6.5 Hz, 2 H), 3.72 (s, 3 H), 3.73 (s, 0.06 H, cis isomer), 4.45 (dt, J = 5.5, 1.5 Hz, 2 H), 4.86 (dt, J = 7.5, 5.5 Hz, 1 H), 5.27 (dq, J = 10.5, 1.5 Hz, 1 H), 5.37 (dq, J = 17, 1.5, 1 H), 6.03 (ddt, J = 17, 10.5, 1.5 Hz), 6.66 (m, 2 H), 6.77 (m, 1 H); mass spectrum, m/e 336 (100, M^+), 273 (28), 263 (42), 189 (24), 177 (64), 161 (28), 147 (18), 91 (12), 59 (10), 55 (10). Anal.: C, H.

Direct Conversion of 23 to 27. A solution of 18.5 g (66.0 mmol) of **23** and 25.0 g (74.8 mmol) of methyl (triphenylphosphoranylidene)acetate in 100 mL of THF was heated at reflux for 4 h. Then 100 mL of methanol and 5 mL (52 mmol) of piperidine were added, and heating was continued for 2 h. The solution was concentrated, and the residue was dissolved in ether. The solids were removed by filtration, and the filtrate was concentrated and purified by flash chromatography (10-cm column) with 25% ethyl acetate–hexane to afford 19.0 g (86%) of a pale orange oil that was spectroscopically identical with **27** that was prepared by the two-step procedure.

Methyl (2*R,3*S**)-[3-(2-Hydroxyethyl)-2,3-dihydro-5-(2-propenyloxy)-2-benzofuranyl]acetate (31).** A solution of 18.0 g (53.5 mmol) of **27** in 100 mL of dry methanol was cooled to 0 °C in an ice bath. Then 10 mL (89 mmol) of BF_3–etherate was added, and the solution was stirred at room temperature for 48 h. The solution was neutralized by the addition of saturated $NaHCO_3$ solution, and the mixture was partitioned between ether and saturated $NaHCO_3$ solution. The aqueous layers were sequentially washed with ether, and the combined ether extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10-cm column) with 30% ethyl acetate–hexane to afford 14.6 g (93%) of a pale yellow oil: IR (CH_2Cl_2) 3610, 3060, 2960, 2880, 1745, 1610, 1490, 1445, 1430, 1380, 1250, 1200, 1030, 1000, 940, 880 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.81 (AB, ddt, J = 14, 8.5, 5.5 Hz, 1 H), 1.92 (ddt, J = 14, 5.5, 5 Hz, 1 H), 2.08 (s b, 1 H), 2.73 (AB, dd, J = 16, 7 Hz, 1 H), 2.82 (AB, dd, J = 15, 7 Hz, 1 H), 3.33 (ddd, J = 8.5, 5.5, 4.5 Hz, 1 H), 3.77 (s, 3 H), 3.85 (dt, J = 6, 5.5 Hz, 2 H), 4.51 (ddd, J = 5.5, 1.5, 1 Hz, 2 H), 4.96 (dt, J = 7, 4.5 Hz, 1 H), 5.27 (ddt, J = 10.5, 1.5, 1 Hz, 1 H), 5.38 (ddt, J = 17, 1.5, 1 Hz, 1 H), 6.03 (ddt, J = 17, 10.5, 5.5 Hz, 1 H), 6.69 (m, 2 H), 6.78 (m, 1 H); mass spectrum, m/e 292 (26, M^+), 2.19 (22), 177 (100), 149 (20), 91 (14), 77 (10), 55 (12). Anal.: C, H.

Methyl (2*R,3*S**)-[3-(2-Chloroethyl)-2,3-dihydro-5-(2-propenyloxy)-2-benzofuranyl]acetate (32).** A mixture of 14.4 g (49.2 mmol) of **31** and 20.0 g (76.0 mmol) of triphenylphosphine in 20 mL of acetonitrile was stirred at room temperature until the solid dissolved. Then 10 mL of carbon tetrachloride was added, and the solution was stirred without external cooling for 4 h, until conversion was complete by TLC (30% ethyl acetate–hexane). The solution was concentrated, and the residue was purified by flash chromatography to afford 13.4 g (87%) of a pale yellow oil: IR (CH_2Cl_2) 3060, 2960, 2880, 1745, 1610, 1490, 1445, 1430, 1390, 1210, 1200, 1030, 1000, 940, 880 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.12 (dt, J = 7, 5 Hz, 2 H), 2.63 (AB, dd, J = 16, 6.5 Hz, 1 H), 2.78 (AB, dd, J = 16, 7.5 Hz, 1 H), 3.33 (dt, J = 7, 5 Hz, 1 H), 3.78 (s, 3 H), 3.69 (dt, J = 7, 5 Hz, 2 H), 4.52 (ddd, J = 5, 2, 1.5 Hz, 2 H), 4.89 (ddd, J = 7, 6, 5.5 Hz, 1 H), 5.28 (ddt, J = 11.5, 2, 1.5 Hz, 1 H), 5.37 (ddt, J = 17, 2, 1.5 Hz, 1 H), 6.04 (ddt,

J = 17, 11.5, 5.5 Hz, 1 H), 6.70 (m, 2 H), 6.80 (m, 1 H); mass spectrum, m/e 312 (22, M^+), 310 (68, M^+), 271 (32), 269 (100), 239 (8), 237 (28), 211 (16), 209 (50), 175 (8), 173 (38), 147 (20), 117 (18), 91 (18), 77 (16), 55 (16). Anal.: C, H.

(2*R,3*S**)-[3-(2-Chloroethyl)-2,3-dihydro-5-(2-propenyloxy)-2-benzofuranyl]ethanal (33).** A solution of 13.3 g (42.7 mmol) of **32** in 200 mL of toluene was cooled to −78 °C in a dry ice–isopropyl alcohol bath. The 30 mL (45 mmol) of a 1.5 M solution of DIBAL-H in toluene was added dropwise, and the solution was stirred at −78 °C for 2 h, until reduction was complete. Excess hydride was destroyed by the addition of 10 mL of a 2 M methanolic HCl solution, and solution was partitioned between ether and 0.2 M HCl. The aqueous layer was washed with ether, and the ether extracts were washed sequentially with water and saturated NaCl solution. The combined extracts were dried ($MgSO_4$) and concentrated to afford 11.9 g (98%) of a colorless oil. This material was not purified but used directly in the next step: IR (CH_2Cl_2) 3060, 2960, 2880, 1730, 1490, 1430, 1280, 1230, 1200, 1140, 1030, 1000, 940, 900 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.12 (dt, J = 7, 6.5 Hz, 2 H), 2.74 (AB, ddd, J = 17, 5.5, 1.5 Hz, 1 H), 2.89 (AB, ddd, J = 17, 7.5, 2 Hz, 1 H), 3.29 (dt, J = 7, 4 Hz, 1 H), 3.71 (t, J = 6.5 Hz, 2 H), 4.45 (ddt, J = 5, 2, 1.5 Hz, 2 H), 4.91 (ddd, J = 7.5, 5.5, 4 Hz, 1 H), 5.27 (ddt, J = 10.5, 2, 1.5 Hz, 1 H), 5.38 (ddt, J = 17, 2, 1.5 Hz, 1 H), 6.03 (ddt, J = 17, 10.5, 5.5 Hz, 1 H), 6.71 (m, 2 H), 6.81 (m, 1 H), 9.84 (dd, J = 2, 1.5 Hz); mass spectrum, m/e 282 (14), 280 (48), 241 (30), 280 (50), 241 (32), 239 (100), 177 (34), 157 (28), 147 (52), 119 (32), 105, (34), 91 (76), 77 (60), 65 (50), 55 (86).

(2*R,3*S**)-3-[3-(2-Chloroethyl)-2,3-dihydro-5-(2-propenyloxy)-2-benzofuranyl]-2-[(trimethylsilyl)oxy]-propanenitrile (34).** A solution of 11.9 g (42.2 mmol) of **33** and 0.500 g (8.77 mmol) of KCN in 25 mL of cyanotrimethylsilane was stirred at 20 °C for 24 h until TLC (25% ethyl acetate–hexane) indicated that conversion to the cyanohydrin was complete. The excess cyanotrimethylsilane was removed by distillation under high vacuum, and the residue was taken up in dichloromethane and filtered. The filtrate was concentrated and dried under high vacuum to afford 16.4 g (94%) of an unstable, pale yellow oil that was not purified but was used directly in the next step: IR (CH_2Cl_2) 3020, 2960, 2940, 2860, 2290 (w), 1720 (w), 1600, 1490, 1420, 1380, 1360, 1270, 1230, 1190, 1150, 1025, 1000, 940, 820 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 0.20 (s, 9 H), 1.9–2.1 (m, 4 H), 3.38 (dt, J = 7, 4 Hz, 1 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.45 (dq, J = 5.5, 1.5 Hz, 2 H), 4.72 (dt, J = 6, 2 Hz, 1 H), 4.96 (ddd, J = 7.5, 5.5, 4 Hz, 1 H), 5.27 (dq, J = 10.5, 1.5 Hz, 1 H), 5.38 (dq, J = 17, 1.5 Hz, 1 H), 6.03 (ddt, J = 17, 10.5, 5.5 Hz, 1 H), 6.71 (m, 2 H), 6.81 (m, 1 H); mass spectrum, m/e 381 (0.2, M^+), 379 (0.8, M^+), 309 (22), 307 (70), 268 (27), 266 (100), 239 (42), 197 (32), 195 (30), 161 (22), 147 (28), 119 (14), 92 (28), 77 (22), 55 (34).

(2*R,3*S**)-3-[3-(2-Chloroethyl)-2,3-dihydro-5-(2-propenyloxy)-2-benzofuranyl]-2-(1-ethoxyethoxy)propanenitrile (35).** A solution of 4.12 g (10.0 mmol) of **34** in 20 mL of THF was cooled to 0 °C in an ice bath. Then 10 mL of a 1 M solution of tetrabutylammonium fluoride in THF was added dropwise over 5 min; after addition was complete, 6 mL of trifluoroacetic acid was added, and the solution was stirred at 0 °C for 30 min. Then 5 mL (mmol) of ethyl vinyl ether and 0.5 mL of trifluoroacetic acid were added, and the solution was stirred at room temperature for 6 h, until reaction was complete. Two product spots (diastereomers) could be seen by TLC (10% ethyl acetate–hexane). The solution was partitioned between ether and saturated $NaHCO_3$ solution, and the aqueous layer was washed with ether. The ether extracts were sequentially washed and saturated $NaHCO_3$ solution and then saturated NaCl solution. The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (5-cm column) with 10% ethyl acetate–hexane to afford 2.97 g (78%) of a colorless oil that was a mixture of diastereomers: IR (CH_2Cl_2) 3030, 2950, 2880, 2290 (w), 1600, 1490, 1420, 1280, 1230, 1190, 1140, 1070, 1020, 1000, 935, 890, 850, 800 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.21, 1.24 (t, J = 7.0 Hz, total 3 H), 1.32, 1.34 (d, J = 5.5 Hz, total 3 H), 2.02–2.23 (m, 4 H), 3.15–3.40 (m, 1 H), 3.65 (t, J = 6.5 Hz, 2 H), 3.50–3.80 (m, 2 H), 4.45 (dq, J = 5.5, 1.5 Hz, 2 H), 4.60 (m, 1 H), 4.80 (m, 1 H), 4.90–5.10 (m, 1 H), 5.28 (dq, J = 10.5, 1.5 Hz, 1 H), 5.39 (dq, J = 17, 1.5 Hz, 1 H), 6.04 (ddt, J = 17, 10.5, 5.5 Hz, 1 H), 6.70 (m, 2 H), 6.80 (m, 1 H); mass spectrum, m/e 380 (0.8, M + H), 378 (3, M + H), 309 (12), 307 (40), 241 (16), 239 (52), 197 (36), 195 (34), 161 (26), 147 (44), 119 (22), 91 (50), 77 (44), 65 (46), 55 (100). Anal.: C, H, N.

(4a*R,9b*S**)-3-(1-Ethoxyethoxy)-1,2,3,4,4a,9b-hexahydro-8-(2-propenyloxy)dibenzofuran-3-carbonitrile (36).** A solution of 10.0 g (26.3 mmol) of **35** in 75 mL of THF was cooled to 0 °C in an ice bath. To this was added 40 mL of 1 M solution of sodium hexamethyldisilazide in THF, and the solution was heated at 60 °C for 1 h. A precipitate formed immediately upon addition of the base, and TLC (10% ethyl acetate–hexane) indicated the formation of two products that moved slightly faster than the starting mixture. The mixture was partitioned between ether and water, and the aqueous layer was washed with ether; then the ether extracts were sequentially washed with saturated $NaHCO_3$ solution and saturated NaCl solution. The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography to afford 8.14 g (90%) of a white crystalline powder: mp 87–95 °C; IR (CH_2Cl_2) 3040, 2980, 2960, 2880, 2300 (w), 1750, 1600, 1480, 1420, 1385, 1370, 1280, 1240, 1195, 1150, 1100, 1060, 1020, 1000, 930, 890 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.151, 1.153, 1.17 (t, J = 7.0 Hz, total 3 H), 1.304, 1.312, 1.34 (d, J = 5.5 Hz, total 3 H), 1.6–2.0 (m, 2 H), 2.2–2.5 (m, 2 H), 2.8–3.0 (m, 3 H), 3.40–3.75 (m, 2 H), 3.98, 4.07 (ddd, J = 12.6, 12.4, 3.6 Hz, total 1 H), 4.47 (dq, J = 5.5, 1.5 Hz, 2 H), 5.11, 5.13 (dq, J = 5.5 Hz, total 1 H), 5.28 (dq, J = 10.5, 1.5 Hz, 1 H), 5.39 (dq, J = 17, 1.5 Hz, 1 H), 6.04 (ddt, J = 17, 10.5, 5.5 Hz, 1 H), 6.65–6.73 (m, 2 H), 6.82 (m, 1 H); mass spectrum, m/e 343 (18, M^+), 271 (12), 244 (22), 203 (38), 185 (32), 147 (12), 91 (14), 73 (100), 55 (22). Anal.: C, H, N.

(4a*R,9b*S**)-3-Hydroxy-1,2,3,4,4a,9b-hexahydro-8-hydroxydibenzofuran-3-carbonitrile (37).** A solution of 0.500 g (1.40 mmol) of **36** and 0.020 g (0.110 mmol) of *p*-toluenesulfonic acid in 5 mL of benzene and 2 mL of methanol was heated at reflux for 6 h. The solution was partitioned between ethyl acetate–saturated NaCl solution, and the ethyl acetate layer was dried ($MgSO_4$) and concentrated. The residue was purifed by flash chromatography (2-cm column) with 30% ethyl acetate–hexane and crystallized from ethyl acetate–hexane to afford 0.181 g (56%) of **37** as colorless needles: mp 246–247 °C; IR (KBr) 3250 (b), 2960, 2880, 2450, 2300, 1700, 1590, 1460, 1390, 1370, 1360, 1280, 1250, 1185, 1120, 1080, 1020, 960, 880, 810 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.65–1.90 (m, 1 H), 2.05 (m, 1 H), 2.20–2.40 (m, 3 H), 2.75–3.05 (m, 2 H), 4.11 (dt, J = 12.5, 4.0 Hz), 5.66 (s b, 1 H), 6.65 (m, 2 H), 6.80 (m, 1 H), 7.66 (s b, 1 H); mass spectrum, m/e 231 (100, M^+), 204 (98), 186 (24), 161 (50), 149 (76), 147 (84), 123 (72), 121 (18), 103 (12), 91 (22), 81 (14), 77 (24), 65 (20), 55 (50).

(4a*R,9b*S**)-1,2,3,4,4a,9b-Hexahydro-8-hydroxydibenzofuran-3-one (3b).** A solution of 0.025 g (0.108 mmol) of **37** in 1 mL of dimethyl sulfoxide was heated at 45 °C under 0.1-mm vacuum for 20 min. The solution was concentrated under vacuum, and the residue was crystallized by addition of ether to afford 0.014 g (63%) of white crystals: mp 199–201 °C; IR (KBr) 3450, 3380, 3960, 3840, 1700, 1590, 1460, 1380, 1350, 1185, 1120, 1090, 1000, 950, 860, 820, 780 cm^{-1}; NMR (300 MHz, CD_3CN) δ 1.70 (m, 1 H), 2.10 (m, 1 H), 2.23–2.40 (m, 3 H), 2.65–2.95 (m, 2 H), 4.08 (dt, J = 12.5, 4.0 Hz), 6.64 (m, 2 H), 6.80 (m, 1 H), 7.68 (s b, 1 H); mass spectrum, m/e 204 (100, M^+), 161 (56), 149 (80), 123 (78), 91 (24), 77 (28), 65 (24), 55 (56). Anal.: C, H.

X-ray Crystal Structure Analysis of 3a. Suitable crystals of **3a** ($C_{12}H_{12}O_3$) for X-ray diffraction studies formed from ethyl acetate–hexane with space group symmetry of $P2_1/n$ and cell constants of a = 6.628 (3) Å, b = 9.565 (1) Å, c = 15.601 (2) Å, and β = 92.42 (2)° for Z = 4 and a calculated density of 1.373 g/cm^3. The cyclohexane ring has a slightly twisted boat conformation. The only short intermolecular contact is a hydrogen bond between O14 and O15 with dimensions O14–O15, 2.75 Å; O14–H14, 0.84 Å; O15–H14, 1.91 Å. Experimental details and Tables VIII–X containing the final fractional coordinates, temperaure parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer-generated perspective drawing of **3a** from the final X-ray coordinates.

X-ray Crystal Structure Analysis of 37. Suitable crystals of **37** ($C_{13}H_{13}NO_3$) for X-ray diffraction studies formed from ethyl acetate–hexane with space group symmetry of $R\bar{3}$ and cell constants of $a = b$ = 29.835 (6) Å and c = 7.142 (1) Å for Z = 18 and a calculated density of 1.255 g/cm^3. The cyclohexane ring is in

a chair conformation. The only short intermolecular contact is a hydrogen bond between O15 and N17 with dimensions O15–N17 = 2.86 Å, O15–H15 = 0.81 Å, and N17–H15 = 2.05 Å. Experimental details and Tables XVII–XIX containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 2 is a computer-generated perspective drawing of **37** from the final X-ray coordinates.

Registry No. **3a**, 126665-91-6; **3b**, 126665-92-7; **5**, 126783-84-4; **8**, 126665-93-8; **11**, 98677-96-4; **12** (isomer 1), 126693-82-1; **12** (isomer 2), 126785-14-6; **13**, 126665-94-9; **14**, 126665-95-0; **15**, 126665-96-1; **16**, 126665-97-2; **17**, 126665-98-3; **18**, 71159-78-9; **19**, 92252-29-4; **21**, 109066-05-9; *cis*-**22**, 126665-99-4; *trans*-**22**, 126666-00-0; *cis*-**23**, 126666-01-1; *trans*-**23**, 126666-02-2; **24**, 126666-03-3; **25**, 126666-04-4; *trans*-**26**, 126666-05-5; *cis*-**26**, 126666-06-6; *trans*-**27**, 126666-07-7; *cis*-**27**, 126666-08-8; **28**, 126666-09-9; **29**, 126666-10-2; **30**, 126693-83-2; **31**, 126666-11-3; **32**, 126666-12-4; **33**, 126666-13-5; **34**, 126666-14-6; **35**, 126666-15-7; **36**, 126666-16-8; **37**, 126666-17-9; hexanal, 66-25-1; benzoquinone, 106-51-4.

Supplementary Material Available: Experimental procedures for preparation of **22**, **24**, **26**, **28**, **29**, and **30** and for the isomerization of **30** to **28**, tables of the MM2/MM2X parameters used in the energy minimization for **10**, **26**, and **27**, and tables of the atomic positional and thermal parameters, bond distances, and bond angles for **3a**, **14**, **16**, and **37** (27 pages). Ordering information is given on any current masthead page.

Chemistry of Dioxenium Cations. Synthetic and Mechanistic Studies on the Stereocontrolled Formation of Tetrahydropyrans from Homoallylic Alcohols and Ortho Esters

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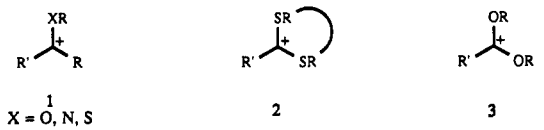
Despite their long history, dioxenium cations are underutilized reactive synthetic intermediates. It was found that ortho esters and homoallylic alcohols in the presence of Lewis acids provide 4-heterosubstituted pyranosides in a stereoselective manner. The mechanistic course of events was supported by control experiments and synthesis of a putative mixed ortho ester intermediate which exhibited identical reactivity. A transition state for termination of the dioxenium cation–olefin cyclization is proposed, involving intramolecular delivery of chloride by a coordinated tin species. Structure–reactivity relationships indicate that a cation-stabilizing substituent (alkyl or alkoxy) at the internal position of the olefin is required for cyclization. A variety of 3-alkyl-substituted homoallylic alcohols cyclize cleanly to substituted 2-alkoxytetrahydropyrans in good yield. β-silyloxy silyl enol ethers were found to smoothly provide 4-oxotetrahydropyranosides when subjected to the same reaction conditions. For these substrates, the course of the cyclization proceeds in a different manner involving a rapid intermolecular Mukaiyama aldol condensation followed by transacetalization.

Introduction

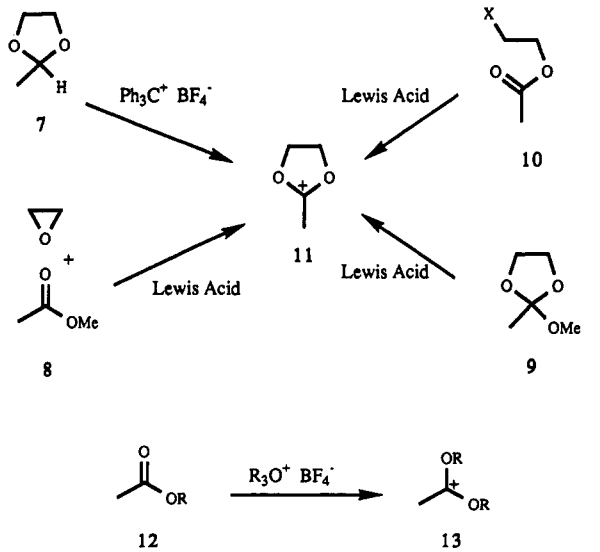
Heteroatom-stabilized carbocations **1** have enjoyed much success as reactive intermediates in organic chemistry. Such species react readily with a wide variety of nucleophilic substances in the formation of new carbon–carbon and carbon–heteroatom bonds. In particular, carbocations stabilized by a single oxygen, nitrogen, or sulfur atom have been utilized extensively as initiators of cation–olefin cyclization processes. Much less well-studied are reactive intermediates in which two heteroatoms stabilize a cationic center. Various aspects of dithienium cation (**2**) chemistry



1 X = O, N, S **2** **3**

including addition to olefins have been studied at various times by a number of groups.[1] The lack of systematic study of the corresponding chemistry of dioxenium cations[2] (**3**) is surprising in view of the greater frequency of occurrence of oxygenated functionality in natural products chemistry. In this paper, we describe in detail our studies[3] which provide some insights on the general reactivity and synthetic utility of dioxenium cations in cation–olefin

Scheme I. Methods of Generating Dioxenium Cations



7 **10** **11** **8** **9** **12** **13**

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