Furannulation Strategy for Synthesis of the Naturally Occurring Fused 3-Methylfurans: Efficient Synthesis of Evodone and Menthofuran and Regioselective Synthesis of Maturone via a Lewis Acid Catalyzed Diels-Alder Reaction. Some Comments for Its Mechanistic Aspects

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Fused 3-methylfurans are readily obtained by the reaction of allenic sulfonium salt 1 and the enolate anions of cyclic 1,3-dicarbonyl compounds in two steps. Using these fused 3-methylfuran compounds as intermediates, furanoterpenoids such as menthofuran (8) and evodone (**4b**) are synthesized efficiently. Moreover, maturone (**15**) is also obtained regioselectivity by Lewis acid catalyzed Diels-Alder reaction of benzofuranquinone (**12**) with piperylene. In the context with the regioselectivity observed in the Diels-Alder reaction of **12**, semiempirical molecular orbital calculations are applied to gain its theoretical interpretation based upon frontier molecular orbital theory and transition state analysis.

Introduction

Fused ring furans are frequently present in terpenoids arising from plants and marine organisms. Their novel structure and biological activities have stimulated considerable synthetic efforts.[2] Biogenetically, many of them, like furanoeremophilanes, possess a 3-methylfuran structure (fused 3-methylfuran ring system) as a common structural unit. This requires some ingenuity in furanoterpenoid synthesis because of the difficulty in direct introduction of a methyl group at the 3-position of the furan ring. Thus, construction of the fused furan accompanied by introduction of a 3-methyl substituent offers an effective route to furanoterpenoids.[3] We now wish to describe a convenient synthesis of fused 3-methylfurans by the reaction of allenic sulfonium salt 1 with enolate anions of cyclic 1,3-dicarbonyl compounds. The results of this work may provide important intermediates leading to the naturally occurring furanoterpenoids such as evodone (**4b**), menthofuran (8), and maturone (**15**).

Result

Syntheses of Fused 3-Methylfurans and 3-(Hydroxymethyl)furans. It is known that allenic sulfonium salt 1 is a reactive electrophile and reacts with enolate anions of an acyclic β-keto ester, a β-keto sulfone, and a β-diketone to afford substituted furans in high yields in one step.[4] Now, we planned to take advantage of this methodology for construction of the fused 3-methylfurans. Allenic sulfonium salt 1, which was easily obtained by the reaction of propargyl bromide and dimethyl sulfide,[5] was added to an ethanolic solution of cyclohexane-1,3-dione (**2a**) and sodium ethoxide. This mixture was reacted for several hours at ambient temperature to afford **3a** as a major product. The ^{1}H NMR showed the characteristic peaks of olefinic protons at δ 5.65 (1H, t, J = 3.0 Hz) and 4.81 (1H, t, J = 3.0 Hz) and methylene protons adjacent to oxygen atom at δ 5.06 (2H, t, J = 3.0 Hz). Apparently, **3a** was formed by addition of an enolate at the carbon atom to the central carbon of 1 followed by ring closure on the oxygen atom with the elimination of dimethyl sulfide.[6] Batty *et al.* reported that reaction of acyclic β-diketone compounds and 1 directly afforded 3-methylfuran compounds and did not isolate exomethylenic compounds such as **3a**.[4,7] Compound **3a** was somewhat unstable and easily isomerized to 3-methylfuran **4a** in 94% yield by treatment with *p*-TsOH (Scheme I). Alternatively, this reaction was performed at reflux and subsequently treated with *p*-TsOH without isolating **3a**, leading to **4a** in 75% yield.

Similarly, reaction of 1 with various cyclic 1,3-dicarbonyl compounds (**2b-e**) afforded **4b-f** in good yields as summarized in Table I. Interestingly, evodone (**4b**),[8] a furanomonoterpene isolated from *Evonia hortensis*, was rapidly synthesized in 75% yield from **2b** (entry 2). 4-Hydroxycoumarin (**2d**) gave a furanocoumarin **4d** in 50% yield (entry 4). Furthermore, *trans*-decalin-1,3-dione (**2e**)[9]

(1) Toyohashi University of Technology.

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(3) (a) Lee, J.; Li, J-H.; Oya, S.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5301. (b) Padwa, A.; Ishida, M.; Muller, C. H.; Murphree, S. S. *Ibid.* **1992**, *57*, 1170. (c) Kobayashi, K.; Shimizu, H.; Sasaki, A.; Suginome, H. *Ibid.* **1991**, *56*, 3204. (d) Jacobi, P. A.; Selnick, H. G. *Ibid.* **1990**, *55*, 202 and refs cited therein. (e) Srikrishna, A.; Krishnan, K. *Tetrahedron Lett.* **1988**, *29*, 4994. (f) Honan, M. C. *Ibid.* **1985**, *26*, 6393. (g) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 3728. (h) Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1978**, *26*, 3704. (i) Bohlmann, F.; Förster, H-J.; Fischer, C-H. *Liebigs Ann. Chem.* **1976**, 1487.

(4) (a) Batty, J. W. *J. Chem. Soc. Chem. Commun.* **1971**, 534. (b) Batty, J. W.; Howes, P. D.; Stirling, C. J. M. *J. Chem. Soc. Perkin Trans. 1* **1973**, 65.

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(7) Recently, exomethylenic compound such as **3a** was reported by other groups: (a) Brown, D. S.; Paquette, L. A. *J. Org. Chem.* **1992**, *57*, 4512. (b) Mandai, T.; Tsuji, J. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 108.

(8) Birch, A. J.; Rickards, R. W. *Aust. J. Chem.* **1956**, *9*, 241.

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Scheme I

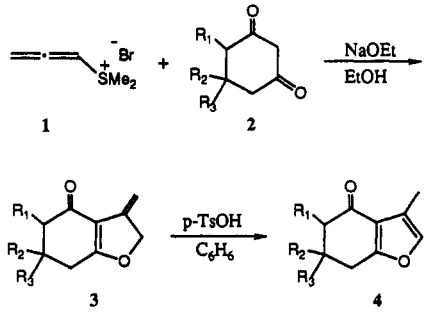
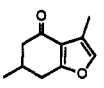
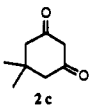
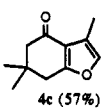
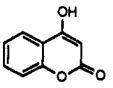
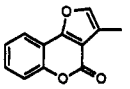
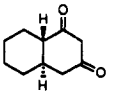
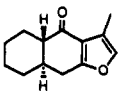
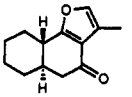
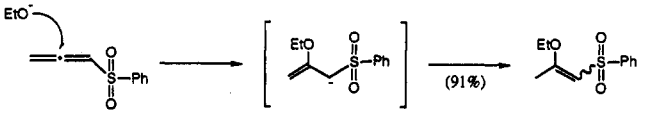


Table I. Fused 3-Methylfuran Synthesis

entry	1,3-dicarbonyl compound	furan (yield)[a]
1	 2a	 4a (75%)
2	 2b	 4b (75%)
3	 2c	 4c (57%)
4	 2d	 4d (50%)
5	 2e	 4e (21%)  4f (35%)

[a] Isolated yield after acid isomerization without purification of the intermediate 3.

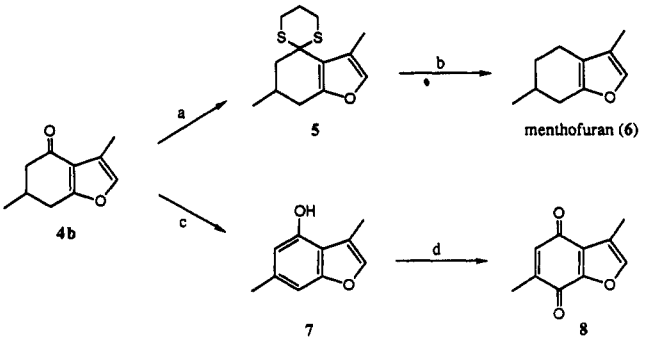
Scheme II



afforded a mixture of two regioisomers 4e and 4f in 35 and 21% yields, respectively (entry 5). Spectral data suggested that the two products were both tricyclic furans. The enol silyl ether of the major isomer showed the signal of the olefinic proton as a broad singlet at δ 4.50 in the ^{1}H-NMR spectrum, which indicated the structure of the major isomer to be 4f (entry 5). In contrast, the reaction of phenylsulfonylallene with the enolate anion of 2c under similar conditions did not afford a fused furan compound and only resulted in the addition of ethoxide anion to the central carbon atom of sulfonylallene (Scheme II).[10]

Compound 4 could be transformed into some important intermediates in synthesis of furanoterpenoids by using the ketone group (Scheme III). Thus, 4b was converted to menthofuran (6),[11] a toxic metabolite of pulegone.[12]

Scheme III[a]



[a] Reagents and conditions: (a) $HS(CH_2)_3SH$, $Zn(OTf)_2$, CH_2Cl_2, room temperature, 85%; (b) Raney Ni, EtOH, reflux, 55%; (c) 10% Pd/C, *p*-cymene, 200 °C, 92%; (d) Fremy's salt, EtOH–KH_2PO_4 buffer, 0 °C, 69%.

Reduction of the thioketal of 5 using Raney nickel gave 6 in 55% yield. On the other hand, 4 could be converted to benzofuranquinone which was a useful dienophile of Diels–Alder reaction in synthesis of linear tricyclic furanoterpenoids. Compound 4b was oxidized to phenol 7 in 92% yield, which was further oxidized to 3,6-dimethylbenzofuran-4,7-quinone (8) by Fremy's salt in 69% yield.[13]

In general, it was difficult to isolate 3 because of its propensity to isomerize to 3-methylfuran 4. However, in the case of reaction of 1 with 2a at room temperature, pure 3a was isolated in 50% yield after careful workup and chromatographic separation. The exomethylene moiety of 3a showed the high reactivity and readily reacted with *N*-bromosuccinimide (NBS) to give 3-(bromomethyl)-furan 9 in 68% yield. Hydrolysis of 9 with alkaline solution afforded 3-(hydroxymethyl)furan 10a in 75% yield. On the other hand, treatment of 3a with monoperoxyphthalic acid magnesium salt (MMPP),[14] gave 10a smoothly in one step (Scheme IV).

Compound 10a could be also converted to benzofuranquinone 12 in a similar manner. After protection of hydroxyl group of 10a under standard conditions, 10b was transformed into the β-keto sulfoxide 10c by use of methyl benzenesulfinate,[15] which was easily converted to the phenol 11a via syn-elimination of the sulfoxide group. After deprotection of 11a, the phenol 11b was converted to 12 by Fremy's salt in 69% yield (Scheme IV).

Synthesis of Maturone. Next, we have investigated to synthesize furanosesquiterpenoid maturone(15)[16,17] as part of our research program.[18] Maturone was isolated from Mexican plant, *Cacalia decomposita*, the root extract of which has been used for the treatment of diabetes and other deseases. The synthesis of maturone has already been achieved by Ghera *et al.* They constructed the linear tricyclic skeleton of maturone by a regioselective annulation between an aromatic bromo sulfone and γ-lactone.[19] Linear tricyclic furan structure of maturone could also be derived from benzofuranquinone 12 as a dienophile in a Diels–Alder reaction.

(9) Cuang, C-K.; Tien, Y-L. *Chem. Ber.* **1936**, *69*, 25.
(10) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley & Sons, Inc.: New York, 1984.
(11) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occuring Compounds, Terpenes*; Academic Press: New York, 1972; Vol. II.
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(13) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.
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(15) Monterio, H. J.; De Souza, J. P. *Tetrahedron Lett.* **1975**, 921.
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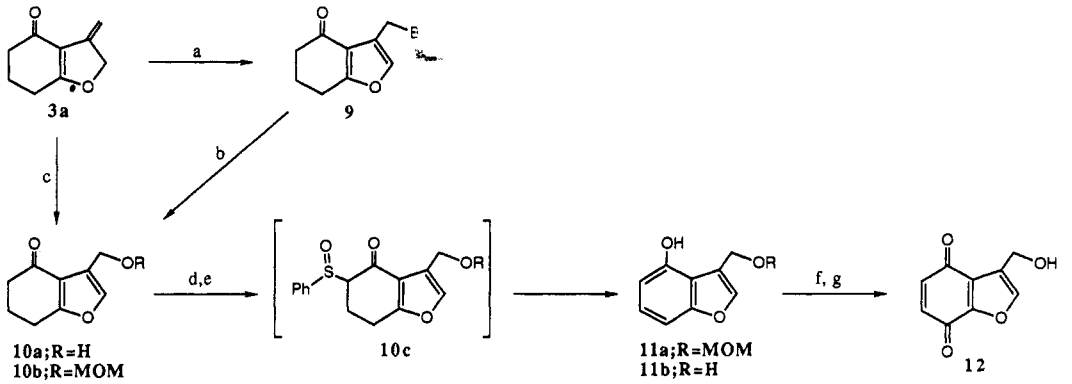
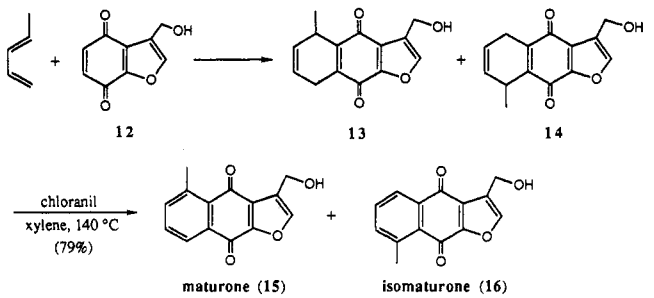
(17) (a) Brown, P. M.; Thomson, R. H. *J. Chem. Soc. C* **1969**, 1184. (b) Kakisawa, H.; Inouye, Y.; Romo, J. *Tetrahedron Lett.* **1969**, 1929.
(18) Aso, M.; Sakamoto, M.; Urakawa, N.; Kanematsu, K. *Heterocycles* **1990**, *31*, 1003.
(19) Ghera, E.; Maurya, R.; Ben-David, Y. *Tetrahedron Lett.* **1986**, *27*, 3935.

Scheme IV[a]



[a] Reagents and conditions: (a) NBS, DME/H_2O, 0 °C, 68%; (b) $NaHCO_3$, THF, reflux, 75%; (c) MMPP, Bu_4NI, CH_2Cl_2/H_2O, 0 °C, 78%; (d) MOMCl, $(i\text{-}Pr)_2NEt$, THF, room temperature, 95%; (e) methyl benzenesulfinate, NaH, THF, 50 °C, and then benzene reflux 82%; (f) trace concd HCl, MeOH, reflux, 84%; (g) Fremy's salt, EtOH–KH_2PO_4 buffer, 0 °C, 69%.

Scheme V



Compound **12** reacted with piperylene in methylene chloride at room temperature to give the cycloadducts, which were oxidized by air to the mixture of regioisomers **13** and **14**. Aromatization of these isomers without separation gave a mixture of maturone (**15**) and isomaturone (**16**) (Scheme V). Although separation of **15** and **16** by column chromatography was unsuccessful, however, the ratio of isomers could be determined by ^1H NMR spectroscopy. The signals of the aromatic methyl group of **15** and **16** were observed at δ 2.81 and 2.83, respectively, and the ratio was determined by comparison of integration of these peaks. Unfortunately, under uncatalyzed conditions the regioselectivity of the cycloaddition was low and the amounts of **15** and **16** formed were almost the same (δ 2.81/2.83 = 1.2:1).

Diels–Alder reactions of quinone derivatives (*p*-benzoquinone, naphthoquinone, quinolinequinone, etc.) that are catalyzed by Lewis acids are known to exhibit higher regioselectivity compared with the corresponding thermal reactions, and their theoretical studies of the regioselectivity are also well documented.[20] However, the Lewis acid catalyzed Diels–Alder reaction of benzofuranquinone has scarcely been studied and few examples have been reported.[3i] For the regioselective maturone synthesis, the Diels–Alder reaction of benzofuranquinone **12** with piperylene was examined under Lewis acid catalyzed conditions. The results of the cycloaddition reaction in the presence and absence of Lewis acid were summarized in Table II. In the presence of $BF_3\cdot Et_2O$ as a catalyst, the reaction proceeded smoothly and gave higher regioselectivity compared with the uncatalyzed reaction. Interestingly, the addition of the excess of $BF_3\cdot Et_2O$ (3 equiv) reversed the ratio of **15** and **16**. On the other hand, using $TiCl_2(Oi\text{-}Pr)_2$ catalyst, which was freshly prepared from $TiCl_4$ and $Ti(Oi\text{-}Pr)_4$,[21] resulted in higher regioselectivity than $BF_3\cdot Et_2O$ catalyst. It is noteworthy that a ratio of cycloadducts as high as 20:1 could be attained when the reaction was performed at −50 °C in the presence of 0.5 equiv of $TiCl_2(Oi\text{-}Pr)_2$. The major isomers in $TiCl_2(Oi\text{-}Pr)_2$-catalyzed reactions could be easily isolated by recrystallization from acetone–*n*-hexane, and its physical and spectral data were identical with those of maturone.[22]

Table II. Diels–Alder Reaction of Benzofuranquinone 12 with Piperylene under Lewis Acid Catalyzed Conditions

Lewis acid	equiv of Lewis acid	temp (°C)	time[a]	yield (%)	ratio 15/16
none [in CH_2Cl_2]		rt	4 d	96	1.2:1
none [in toluene]		110	3 d	78	1.3:1
none [in EtOH]		rt	4 d	79	1:2
$BF_3\cdot Et_2O$	0.5	−40	6 h	61	3.3:1
	1.0	−40	4 h	85	2:1
	3.0	−40	3 h	96	1:1.6
$Ti(Oi\text{-}Pr)_4$	1.0	0	1 d	27	1:1.2
$TiCl_2(Oi\text{-}Pr)_2$	0.5	−50	17 h	66	20:1
	1.0	−40	3 h	60	12.5:1

[a] d: day, h: hour.

Having accomplished an efficient synthesis of maturone *via* a regioselective Diels–Alder reaction, we turned out attention to the understanding of regioselectivity shown by the experimental results. In order to elucidate the orientation of the nature of the regioselectivity, we first tried a theoretical interpretation using molecular orbital calculations.

Computational Technique. Semiempirical molecular orbital calculations were performed with AM1 Hamiltonian[23] implemented in MOPAC program.[24] All geometries were fully optimized. Transition states were located by

(20) (a) Ohgaki, E.; Motoyoshoya, J.; Narita, S.; Kakurai, T.; Hayashi, S.; Hirakawa, K. *J. Chem. Soc. Perkin Trans. 1* **1990**, 3109. (b) Dannenberg, J. J.; Franck, R. W. *J. Org. Chem.* **1985**, *50*, 2635. (c) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554. (d) Tou, J. S.; Reusch, W. *J. Org. Chem.* **1980**, *45*, 5013. (e) Boeckmann, R. K., Jr.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098. (f) Kelly, T. R.; Montury, M. *Tetrahedron Lett.* **1978**, 4311. (g) Stojanac, Z.; Dickinson, R. A.; Stajanac, N.; Woznow, R. J.; Valenta, Z. *Can. J. Chem.* **1975**, *53*, 616.

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(22) We thank Professor E. Ghera, the Weizmann Institute of Science, for ^1H NMR spectral data of maturone.

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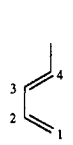
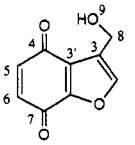
(24) Stewart, J. J. P. JCPE P044, version 6, 1990.

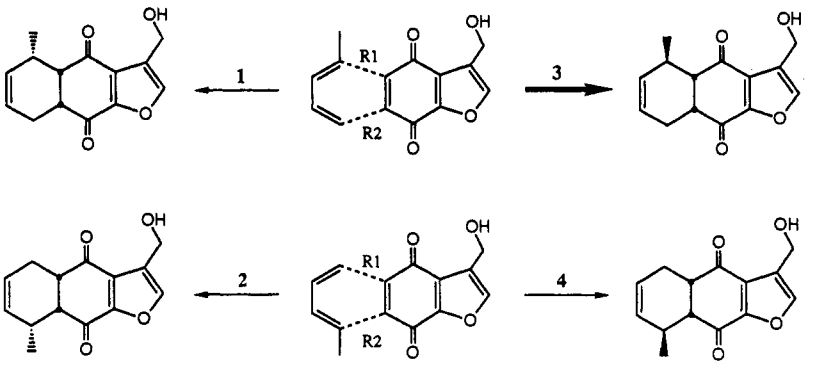
Table III. FMO Energies and Coefficients of Piperylene and Benzofuranquinone 12[a]

		HOMO coefficients					LUMO coefficients			
method	HOMO, eV	C-1	C-2	C-3	C-4	LUMO, eV	C-4	C-5	C-6	C-7
AM1[b]	-9.059	0.526	0.370	-0.468	-0.545	-1.918	0.338	0.351	-0.339	-0.354
CNDO/2[c]	-	0.543	0.369	-0.450	-0.511					
STO-3G[d]	-7.216	0.502	0.373	-0.441	-0.515					

[a] The conformer of 12 having the lowest heat of formation is used here. Dihedral angle of O_9–C_8–$C_{3'}$–$C_{3'}$ is 58.36°. [b] LUMO energy of piperylene is 0.445 eV and HOMO energy of 12 is -10.048 eV. [c] Reference 30. [d] Obtained with SPARTAN.[28]

Scheme VI. Diels–Alder Reactions of 12 with Piperylene (reaction 3 is most favorable based on computational evidence in several cases)



the reaction coordinate method,[25] and refined by the Non-Linear Least Squares gradient minimization routine (NLLSQ option)[26] and/or eigenvector-following routine (TS option).[24] When gradients are small and decrease slowly, TS option proved much faster and more reliable than NLLSQ. Transition states were characterized by confirming the only one negative eigenvalue in the Hessian matrix.[27] STO-3G calculations were performed using SPARTAN program.[28]

Explanation of the Orientation in the Uncatalyzed Reaction by FMO Theory. The regioselectivity in the Diels–Alder reaction has been successfully explained in terms of Frontier Molecular Orbital theory (FMO).[29] Table III presents HOMO coefficients and energies of piperylene as obtained by AM1, CNDO/2, and STO-3G. Contrary to the CNDO/2 results which had indicated a larger coefficient C-1 than at C-4 of piperylene,[30] our STO-3G calculations reveal the reverse trend. AM1 gives the same relative magnitude as STO-3G. For this reason and also in order to handle such large molecules as 12, we use the AM1 results for these and all other molecules mentioned in this work. In benzofuranquinone 12, the magnitude of the LUMO coefficient at C-5 is slightly greater than C-6. Hence the reaction paths 1 and 3 in Scheme VI will be more favorable than reaction paths 2 and 4. We expect, however, that the regioselectivity of this reaction is low because of the small difference of these coefficients. This observation is consistent with the observed regioselectivity of Diels–Alder reaction carried out in methylene chloride in the absence of catalyst (Table II).

Solvent Effects. As interesting reversal of the regioselectivity has been observed when the reaction medium was changed from methylene chloride to ethanol (Table II). We studied the effects of intramolecular OH···O (C-4 carbonyl oxygen) hydrogen-bond formation[31] in 12 upon its LUMO coefficients, hoping to rationalize the experimental observation in terms of the destruction of the intramolecular hydrogen bond with ethanol. However, no clear result emerged. In the conformer 12 as depicted in Table III, AM1 results showed that the distance between the C-4 carbonyl oxygen and the O-9 hydroxyl hydrogen was 2.1 Å, which is too long to construct the intramolecular hydrogen bond. The observed reversal of selectivity may be the results of overlapping causes involving the differential solvation of the polar transition state.[32] The effect of solvent would be larger in the polar TS than in GS. We assume that this effect probably influences the observed change of regioselectivity.

Explanation of the Orientation in the Catalyzed Reaction by FMO Theory. The well-known catalysis of Lewis acid on the Diels–Alder reaction has manifested itself in the present work in a dramatic way (Table II). In order to see if the catalytic effect can be accounted for by studying FMO's of the Lewis acid complexes with a dienophile, AM1-calculations of all possible 1:1 and some

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(26) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161.
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(28) Carpenter, J. E.; Baker, J.; Hehre, W. J.; Kahn, S. D. SPARTAN User's Guide, 1990.
(29) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley & Sons, Inc.: New York, 1976.
(30) The coefficients of piperylene are quoted from ref 20a.
(31) In IR, benzofuranquinone 12 showed two split C=O absorption bands corresponding to two carbonyl groups at 1660 and 1680 cm^{-1}. In the case of the hydroxyl group protected silyl ether of 12 and 3-methylbenzofuran-4,7-quinone, the sharp singlet absorption band was observed at 1670 cm^{-1}. On the other hand, in ^{1}H-NMR ($CDCl_3$), under the high concentration condition, the methylene protons at 8-position of 12 showed a sharp signal. However, under the low concentration, a somewhat broad signal was observed. This phenomenon probably is due to the inhibition of free rotation of hydroxymethyl group by the formation of intramolecular hydrogen bond under the low concentration conditions.
(32) Cramer, C. C.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8305.

Scheme VII. BF_3 Complexes of Benzofuranquinone 12

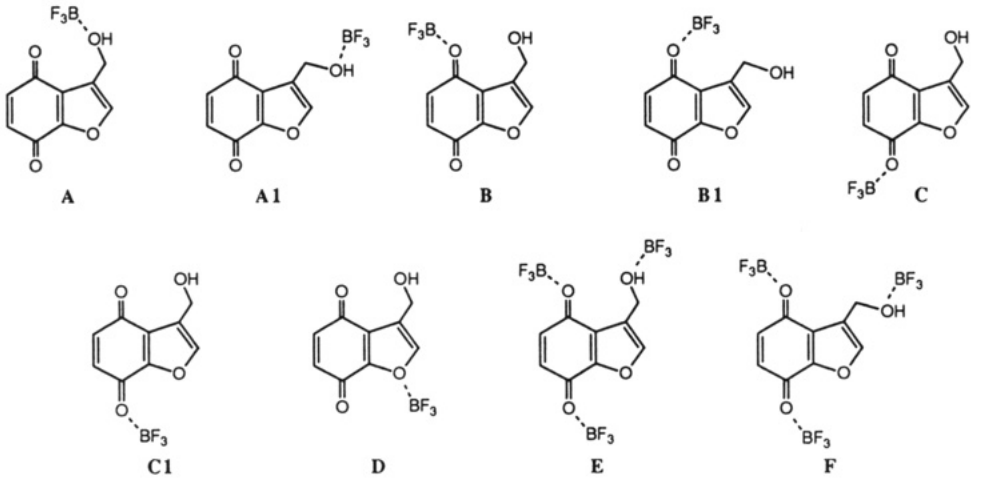


Table IV. FMO Energies and Coefficients of BF_3–12 Complexes by AM1[a]

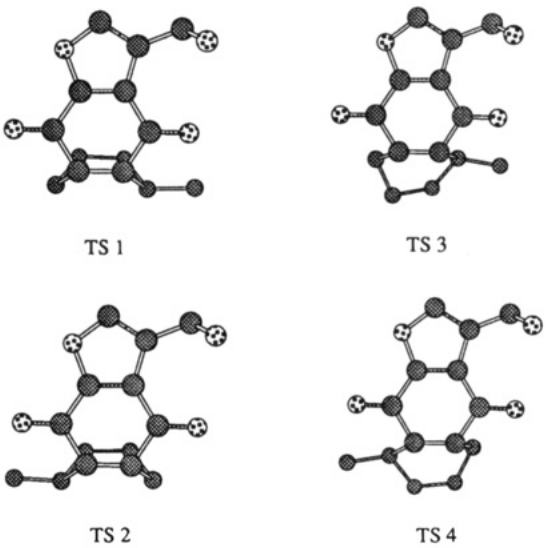
	LUMO, eV	C-4	C-5	C-6	C-7
A	−2.161	−0.343	−0.342	0.335	0.349
A1	−2.074	−0.330	−0.346	0.331	0.354
B	−2.451	−0.408	−0.317	0.355	0.325
B1	−2.198	−0.374	−0.336	0.344	0.340
C	−2.467	−0.310	−0.355	0.299	0.417
C1	−2.403	−0.314	−0.356	0.309	0.408
D	−2.100	−0.336	−0.336	0.329	0.345
E	−3.053	−0.384	−0.322	0.326	0.375
F	−2.910	−0.353	−0.335	0.309	0.394

[a] See Scheme VII for the structures of complexes.

of the 3:1 BF_3–12 complexes have been carried out (Scheme VII and Table IV).[33]

BF_3–12 complexes generally give LUMO levels at −2 to −3 eV which are significantly lower than the free dienophile 12 (−1.9 eV, Table III). This trend accords with the observed increase in the ease of reaction. It has been proposed that the Lewis acid increases the difference in the coefficients of the interacting FMO's as well.[29] We find that relative magnitudes of LUMO coefficients at C-5 and C-6 vary dramatically among the complexes depending on the position of BF_3 in the complex. Among the calculated 1:1 orientational isomers, complex C is remarkable with the lowest LUMO energy and the largest difference between C-5 and C-6 coefficients. Thus, we assume that complex C reacts with piperylene faster than do its competitors. Even though the Lewis basicity of carbonyl oxygen at C-4 may be greater than that of C-7,[34] the complex C with BF_3 attached to C-7 (and perhaps the closely related complex C-1 as well) can be responsible for the observed high regioselectivity favoring **15** in the addition of piperylene to **12** at low BF_3 concentrations (Table II). Addition of excess BF_3-catalyst not only reduced the selectivity but also reversed the orientation of piperylene. These effects should be attributed to multiple coordination of catalysts to **12** like E and F (Scheme VII). Unfortunately, we cannot explain this effect by FMO theory alone: the magnitude of coefficient of C-5 for multi-complex F is larger than that of C-6, which would have predicted a selectivity disagreeing with experimental data. Here again, we suggest that the effects of excess BF_3 must be too complicated to explain with our simplistic technique.

Scheme VIII. Transition Structures of Diels–Alder Reactions of 12 and Piperylene



On the other hand, $TiCl_2(Oi\text{-}Pr)_2$-catalyzed reaction gave the highest regioselectivity (maturone/isomaturone = 20:1!) compared with the reaction catalyzed by $BF_3{\cdot}Et_2O$. $TiCl_2(Oi\text{-}Pr)_2$ may interact with **12** through the chelation complex, i.e. alkoxy exchange between the hydroxyl group of **12** and *i*-PrOH followed by coordination with C-4 carbonyl oxygen. However, if such a species forms, the predicted regioselectivity based upon FMO theory is opposed to the experimental results. Thus, we assume that, as well as in the low concentration of $BF_3{\cdot}Et_2O$-catalyzed reaction, the coordination of $TiCl_2(Oi\text{-}Pr)_2$ to C-7 carbonyl oxygen is responsible for the high regioselectivity shown by experiments. To observe the interaction of **12** with $TiCl_2(Oi\text{-}Pr)_2$, ^{1}H-NMR study was attempted under low temperature (−50 °C); however, no informative result was obtained.

Calculations of Transition States. The options for searching transition states implemented in MOPAC promoted us to study the transition states (TS) of reactions 1–4 (TS1–TS4, Scheme VIII). The activation parameters and bond lengths of TS's in the uncatalyzed reaction are summarized in Table V. Due to the lack of symmetry and

(33) Distribution of BF_3 on various basic sites of **12** can be in principle evaluated by the relative energies of geometry-optimized isomers which differ in the orientation of BF_3. However, inferring the stabilities of these polar complexes in polar solvent from the vapor-phase energies seems too robust and we focus here only on the FMO features (Table IV).

(34) Charge density of carbonyl oxygen atom of C-4 is calculated to be −0.273 and that of C-7 is −0.229 by AM1.

Table V. AM1-Calculated Bond Distances, Dipole Moments, and Activation Parameters of Transition States in the Diels–Alder Reaction between 12 and Piperylene at 298K[a]

TS[b]	R1	R2	R	ΔR	ΔH‡	ΔS‡	ΔG‡	dipole moment
1	2.231	2.056	2.144	0.175	26.29	−55.1	42.71	3.57
2	2.051	2.238	2.145	0.187	26.15	−54.9	42.50	3.68
3	2.262	2.028	2.145	0.234	25.37	−54.7	41.67	3.73
4	2.021	2.272	2.147	0.251	25.16	−54.6	41.43	3.84

[a] R1 and R2 are the lengths of incipient C–C bonds. *R* is the average and Δ*R* is the difference between *R*1 and *R*2. *R*1, *R*2, *R* and Δ*R* in Å, Δ*H*‡ and Δ*G*‡ in kcal/mol, Δ*S*‡ in cal/K/mol, dipole moment in debye. [b] See Scheme VIII for the drawings of optimized structures.

also for steric reasons, the lengths of two incipient C–C bonds (R1, R2) are unequal in the optimized TS's. The longer of the two incipient bonds is always associated with the more-substituted carbon atoms. We obtained here Δ*H*‡ values directly from the calculated total energies and Δ*S*‡ from the vibration frequencies of TS. The present results do not follow the compensation effect between Δ*H*‡ and Δ*S*‡.[35]

We expected that endo addition (TS1 and TS2) may be more favorable than exo addition (TS3 and TS4) because of the secondary orbital interaction.[36] However, TS3 and TS4 turned out to be slightly more favorable than TS1 and TS2 in terms of activation energy. However TS3 and TS4 have almost the same activation energy, hence the TS theory failed to explain the observed selectivity. However, our results positively indicate that this reaction follows the synchronous concerted mechanisms[37] involving cyclic aromatic TS.

Furthermore, TS calculation was performed with the BF_3-catalyzed reaction in favored reaction paths 3 and 4. BF_3-catalyzed reactions are expected to show lower activation enthalpies than the uncatalyzed reactions. Although the expected tendency indeed appeared, AM1 could not reproduce the observed difference between reaction paths 3 and 4 under the BF_3-catalyzed conditions.

In conclusion, at the level of AM1 calculations, FMO theory rationalizes the regioselectivity of the Diels–Alder reaction of 12 with piperylene in methylene chloride and in the presence of small amounts of BF_3. This theory, however, does not rationalize the effects of solvent and excess BF_3. The transition states calculations do not give the effective informations of the regioselectivity, but do not contradict with the synchronous mechanism under uncatalyzed conditions. However, if this Diels–Alder reaction proceeds with the synchronous concerted mechanism, the effect of solvent, which may be rationalized by polar transition state, cannot be explained well. Thus, concerning the mechanism for this Diels–Alder reaction, TS calculations are in conflict with the assumption derived from the experimental result.

Summary

Using allenic sulfonium salt method for constructing fused 3-methylfurans, we could efficiently synthesize naturally occurring fused furan compounds such as evodone, menthofuran, and maturone. The Lewis acid catalyzed Diels–Alder reaction was applied to attain the regioselective synthesis of maturone, but the changes of regioselectivity observed in the various conditions were not explained completely by semiempirical molecular orbital calculation method. The actual picture of these phenomena is much more complex than our simple expectations. Further application of this direct furannulation method is expected in the synthesis of a variety of furanoterpenoids and now progresses in our laboratory.

Experimental Section

General. The melting point were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were taken on JEOL GX-270 (270 MHz), JEOL FX-100 (100 MHz), and Hitachi R-1500 (60 MHz) spectrometer. The ^{13}C-NMR spectra were recorded on a JEOL GX-270 (67.8 MHz). Chemical shifts are reported in δ units (part per million downfield from Me_4Si). The IR spectra were determined on a JASCO IR A-100 infrared spectrophotometer. The mass spectra (MS) were determined on JEOL D-300 or JEOL DX-300. The elemental analysis were performed on a Yanagimoto MT2 CHN recorder. Analytical thin-layer chromatography (TLC) was performed with E. M. Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm). Nonflash chromatography separations were carried out on E. M. Merck Kieselgel 60 (70–230 mesh) or E. M. Merck aluminum oxide 90 (70–230 mesh) as the stationary phase. Flash chromatography separations were conducted with E. M. Merck Kieselgel 60 (230–400 mesh). All reactions sensitive to moisture or air were performed under argon. Reaction vessels were flame-dried or oven-dried and allowed to cool under inert atmosphere for moisture-sensitive reactions.

3-Methylidene-2,3,4,5,6,7-hexahydrobenzofuran-4-one (3a). A mixture of dimethyl sulfide (2.7 mL, 36.8 mmol) and propargyl bromide (80 wt. %) (4.0 mL, 35.6 mmol) in anhydrous acetonitrile (20 mL) was stirred in a light-protected flask at room temperature. After 16 h, the obtained colorless solid was treated with triethylamine (5.0 mL, 35.9 mmol) and an ethanolic solution (20 mL) of cyclohexane-1,3-dione (2.0 g, 17.8 mmol) and sodium ethoxide (1.21 g, 17.8 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with water, and EtOH was removed in vacuo. The residue was extracted with dichloromethane (×2), and the combined organic layers were washed with brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on alumina (*n*-hexane/ethyl acetate = 15:1) followed by chromatography on silica gel (*n*-hexane/ethyl acetate = 4:1) gave 1.33 g (50%) of **3a** as a colorless solid: mp 62.5–63.0 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 5.67 (t, *J* = 3.0 Hz, 1H), 5.07 (t, *J* = 3.0 Hz, 2H), 4.82 (t, *J* = 3.0 Hz, 1H), 2.64–1.79 (m, 6H); IR ($CHCl_3$) 1650, 1660, 1600, 1430 cm^{-1}; LRMS (EI, 30 eV) *m/z* (rel inten) 150 (M^+, 70), 12 (100). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.79; H, 6.78.

3-Methyl-6,7-dihydrobenzofuran-4(5H)-one (4a). A mixture of dimethyl sulfide (1.5 mL, 20 mmol) and propargyl bromide (80 wt. %) (1.8 mL, 16 mmol) in anhydrous acetonitrile (1.2 mL) was stirred in a light-protected flask at room temperature. After 16 h, the obtained colorless solid was treated with anhydrous EtOH (2 mL) and then an ethanolic solution (20 mL) of cyclohexane-1,3-dione (1.0 g, 8.9 mmol) and sodium ethoxide (0.61 g, 8.9 mmol) was added. The reaction mixture was refluxed for 1 h. The resulting mixture was diluted with water, and EtOH was removed in vacuo. The residue was extracted with dichloromethane (×2), and the combined organic layers were washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the benzene solution (10 mL) of the crude mixture of **3a** was treated with *p*-toluenesulfonic acid (1.7 g, 8.9 mmol). After 1 h, the resulting mixture was quenched with saturated $NaHCO_3$, diluted with water, and extracted with dichloromethane (×2). The combined organic layers were washed with water and brine followed by dring over anhydrous Na_2SO_4. After removal of the solvent in vacuo,

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(36) Alston, P. V.; Ottenbrite, R. M. *J. Org. Chem.* **1975**, *40*, 1111.
(37) (a) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781. (b) Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.* **1984**, *106*, 203. (c) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *Ibid.* **1986**, *108*, 5771. (d) Bernardi, F.; Bottoni, A.; Field, M. J.; Guest, M. F.; Hiller, I. H.; Robb, M. A.; Venturini, A. *Ibid.* **1988**, *110*, 3050.

chromatography on silica gel (*n*-hexane/ethyl acetate = 4:1) gave **4a** as a solid (996 mg, 76%): mp 62.5–63.5 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.07 (br s, 1H), 2.83 (t, J = 6.0 Hz, 3H), 2.19 (d, J = 1.2 Hz, 3H), 2.56–2.04 (m, 4H); IR ($CHCl_3$) 2950, 1660, 1560, 1415, 1410 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 150 (M^+, 94), 122 (100), 94 (55), 66 (21). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.90; H, 6.70.

3,6-Dimethyl-6,7-dihydrobenzofuran-4(5H)-one (4b). 5-Methylcyclohexane-1,3-dione (460 mg, 3.7 mmol) was used as a starting material. By the same procedure described for the synthesis of **4a** and the purification by column chromatography on silica gel (*n*-hexane/ethyl acetate = 6:1), **4b** was obtained as a solid (447 mg, 75%): mp 71–71.5 °C (lit.[8] 73 °C); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.06 (br s, 1H), 2.87–2.10 (m, 5H), 2.18 (d, J = 1.2 Hz, 3H), 1.15 (d, J = 4.8 Hz, 3H); IR ($CHCl_3$) 2950, 1660, 1550, 1430, 1400 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 164 (M^+, 52), 122 (100), 94 (38). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.36. Found: C, 72.98; H, 7.33.

3,6,6-Trimethyl-6,7-dihydrobenzofuran-4(5H)-one (4c). 5,5-Dimethylcyclohexane-1,3-dione (700 mg, 5.0 mmol) was used as a starting material. By the same procedure described for the synthesis of **4b**, **4c** was obtained as an oil (510 mg, 57%): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.08 (br s, 1H), 2.70 (s, 2H), 2.34 (s, 2H), 2.19 (d, J = 1.2 Hz, 3H), 1.13 (s, 6H); IR (neat) 2960, 1680, 1560, 1430, 1410, 1070 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 178 (M^+, 35), 122 (100), 94 (32); HRMS (EI, 30 eV) m/z 178.0988 (M^+, calcd for $C_{11}H_{14}O_2$ 178.0993).

3-Methylfuro[2,3-*c*]chromen-4-one (4d). 4-Hydroxycoumarin (830 mg, 5.1 mmol) was used as a starting material. By the same procedure described for the synthesis of **4b**, **4d** was obtained as a solid (511 mg, 50%): mp 156–157 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.84 (dd, J = 7.6, 1.3 Hz, 1H), 7.53–7.29 (m, 3H), 7.41 (q, J = 1.3 Hz, 1H), 2.37 (d, J = 1.3 Hz, 3H); IR ($CHCl_3$) 1730, 1630 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 200 (M^+, 100). Anal. Calcd for $C_{12}H_8O_3$: C, 72.00; H, 4.03. Found: C, 71.87; H, 4.00.

Reaction of *trans*-Decalin-1,3-dione with 1: (4aβ,8aα)-3-Methyl-5,6,7,8,8a,9-hexahydronaphtho[2,3-*b*]furan-4(4aH)-one (4e) and (5aα,9aβ)-3-Methyl-5a,6,7,8,9,9a-hexahydronaphtho[1,2-*b*]furan-4(5H)-one (4f). *trans*-Decalin-1,3-dione[9] (980 mg, 6.0 mmol) was used as a starting material. By the same procedure described for the synthesis of **4a** and the purification by chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1), **4e** (250 mg, 21%) and **4f** (414 mg, 35%) were each obtained as solids. Spectral data of **4e** is as follows: mp 125.5–127 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.04 (br s, 1H), 2.85 (dd, J = 17.0, 4.5 Hz, 1H), 2.55 (dd, J = 16.9, 10.6 Hz, 1H), 2.43–2.38 (m, 1H), 2.18 (d, J = 1.3 Hz, 3H), 2.07–1.87 (m, 4H), 1.78–1.74 (m, 1H), 1.42–1.12 (m, 4H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 197.0, 166.2, 138.9, 119.9, 119.2, 51.2, 40.8, 34.0, 31.3, 25.8, 25.7, 9.0; IR ($CHCl_3$) 2925, 2850, 1660, 1550, 1420 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 204 (M^+, 67), 161 (21), 122 (100), 94 (29). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.30; H, 7.93.

Spectral data of **4f** is as follows: mp 99–100 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.06 (br s, 1H), 2.54 (ddd, J = 10.9, 10.9, 3.3 Hz, 1H), 2.45 (dd, J = 16.4, 3.4 Hz, 1H), 2.39–2.36 (m, 1H), 2.29 (dd, J = 16.4, 12.7 Hz, 1H), 2.19 (d, J = 1.3 Hz, 3H), 1.96–1.70 (m, 4H), 1.51–1.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 195.4, 169.9, 139.1, 119.8, 119.2, 46.6, 42.6, 41.1, 32.1, 27.1, 25.8, 25.6, 9.0; IR ($CHCl_3$) 2910, 2830, 1650, 1540, 1420 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 204 (M^+, 100), 176 (34), 135 (42). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.32; H, 7.92.

6',7'-Dihydro-3',6'-dimethylspiro[1,3-dithiane-2,4'(5'H)-benzofuran] (5). To a suspension of zinc triflate[38] (640 mg, 1.76 mmol) and 1,3-propanedithiol (0.3 mL, 3.0 mol) in anhydrous dichloromethane (2 mL) was added a dichloromethane (3 mL) solution of **4b** (146 mg, 0.89 mmol). The reaction mixture was stirred for 65 h at room temperature. The resulting mixture was diluted with water and extracted with ether/hexane (1:1 v/v) (×2). The combined organic layers were washed with 2% HCl (×2) and saturated $NaHCO_3$ followed by drying over anhydrous Na_2SO_4. After removal of the solvent and residual propanedithiol in vacuo, chromatography on silica gel (*n*-hexane/ether = 30:1) gave 188 mg (83%) of **5** as a colorless solid: mp 84–85 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.03 (br s, 1H), 3.32–3.08 (m, 2H), 2.90–2.84 (m, 1H), 2.75–2.59 (m, 3H), 2.26 (d, J = 1.3 Hz, 3H), 2.25–2.08 (m, 3H), 1.98–1.80 (m, 2H), 1.12 (d, J = 6.3 Hz, 3H); IR ($CHCl_3$) 2950, 2910, 1610, 1440–1390, 1260 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 254 (M^+, 51), 180 (100), 165 (34). Anal. Calcd for $C_{13}H_{18}OS_2$: C, 61.37; H, 7.13. Found: C, 61.61; H, 7.23.

3,6-Dimethyl-4,5,6,7-tetrahydrobenzofuran (menthofuran) (6). To a solution of **5** (37 mg, 0.145 mmol) in ether (1 mL) was added dropwise an ethanolic solution of Raney nickel W-2 (10 mL), and the mixture was refluxed for 15 min with stirring. The reaction was monitored by TLC (*n*-pentane, detection with Ehrlich's reagent). The resulting mixture was filtered and rinsed with *n*-pentane. The filtrate was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel with *n*-pentane gave 12 mg (55%) of **6** as a colorless oil. The IR and ^{1}H NMR spectra of **6** were consistent with the spectra reported in the literature:[39] HRMS (EI, 30 eV) m/z 150.1026 (M^+, calcd for $C_{10}H_{14}O$ 150.1044).

3,6-Dimethylbenzofuran-4-ol (7). In a sealed tube to a solution of **4b** (150 mg, 0.92 mmol) in *p*-cymene (10 mL) was added 10% Pd–C (190 mg), and it was heated for 12 h at 200 °C. The resulting mixture was filtered and rinsed with ethyl acetate. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate = 5:1) gave 137 mg (92%) of **7** as a colorless solid: mp 92–94 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.18 (br s, 1H), 6.84 (br s, 1H) 6.33 (br s, 1H), 5.13 (br s, 1H, D_2O exchangeable), 3.37 (s, 3H), 3.35 (s, 3H); IR ($CHCl_3$) 3600, 3500–3100, 2900, 1630, 1610, 1580, 1420, 1320, 1240 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 162 (M^+, 100), 161 (52). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.11; H, 6.27.

3,6-Dimethylbenzofuran-4,7-dione (8). A solution of **7** (100 mg, 0.62 mmol) in EtOH (5.7 mL) was cooled to 0 °C, and an ice-cooled aqueous buffer solution of freshly prepared Fremy's salt (430 mg, 1.60 mmol dissolved in 5.7 mL of 0.17 M KH_2PO_4 solution and 21.5 mL of water) was added dropwise over 15 min with stirring at 0 °C. The reaction mixture was stirred for an additional 1 h at 0 °C. After diluting with water, the resulting mixture was extracted with chloroform (×3). The combined organic layers were washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (*n*-hexane/ethyl acetate = 2:1) gave 70 mg (69%) of **8** as a yellow solid: mp 145–147 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.45 (br s, 1H), 6.50 (br s, 1H), 2.27 (s, 3H), 2.12 (s, 3H); IR ($CHCl_3$) 1660, 1530, 1380 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 176 (M^+, 100), 148 (25), 108 (23), 91 (30), 52 (22). Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.98; H, 4.49.

3-(Bromomethyl)-6,7-dihydrobenzofuran-4(5H)-one (9). To a solution of **3a** (190 mg, 1.27 mmol) in DME/H_2O (30 mL, 10:1, v/v) was added freshly recrystallized *N*-bromosuccinimide (250 mg, 1.40 mmol) over 30 min at room temperature with stirring. The mixture was stirred for an additional 30 min during which time the pH is maintained within the range 7.0–8.0 by the addition of 10% $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate (×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (*n*-hexane/ethyl acetate = 4:1) gave 197 mg (68%) of **9** colorless solid: mp 63–64 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.40 (br s, 1H), 4.58 (br s, 2H), 2.87 (t, J = 6.0 Hz, 2H), 2.61–1.80 (m, 4H); IR ($CHCl_3$) 2930, 1660, 1550, 1440, 1260 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 230 (M^+ + 1, 16), 228 (M^+ – 1), 149 (100). Anal. Calcd for $C_9H_9O_2Br$: C, 47.10; H, 3.89. Found: C, 47.19; H, 3.96.

3-(Hydroxymethyl)-6,7-dihydrobenzofuran-4(5H)-one (10a). (A) Hydrolysis of 9. To a solution of **9** (192 mg, 0.84 mmol) in THF (25 mL) was added 10% $NaHCO_3$ solution (10 mL), and the mixture was refluxed for 20 h with stirring. The resulting mixture was cooled to room temperature and extracted with ethyl acetate (×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel

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(*n*-hexane/ethyl acetate = 3:1) gave 104 mg (75%) of **10a** as a colorless solid.

(B) Reaction of 3a with MMPP. To a suspension of **3a** (3.0 g, 20.0 mmol) and tetrabutylammonium iodide (370 mg, 1.0 mmol) in dichloromethane (30 mL) was added dropwise an aqueous solution (40 mL) of monoperoxyphthalic acid, magnesium salt (80%) (13.6 g, 22.0 mmol) over 1 h with stirring at 0 °C. The mixture was stirred for 20 min at 0 °C and an additional 40 min at room temperature during which time the pH is maintained within the range 4.5–6.5 by the addition of aqueous 5% NaOH solution. After quenching with aqueous $Na_2S_2O_3$ solution, the mixture was extracted with ethyl acetate (×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (*n*-hexane/ethyl acetate = 2:1) gave 2.60 g (78%) of **10a** as a colorless solid: mp 66–68 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.23 (br s, 1H), 4.52 (br s, 1H), 4.34 (br s, 1H, D_2O exchangeable), 2.87 (t, J = 6.0 Hz, 2H), 2.65–2.08 (m, 4H); IR ($CHCl_3$) 3600–3200, 2950, 1650, 1560, 1450, 1440, 1260 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 166 (M^+, 100), 138 (47), 137 (34). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 64.93; H, 6.07.

3-(Methoxymethoxymethyl)-6,7-dihydrobenzofuran-4-(5H)-one (10b). To a solution of **10a** (1.50 g, 9.03 mmol) in anhydrous THF (30 mL) was added diisopropylethylamine (9.4 mL, 54.2 mmol) and chloromethyl methyl ether (3.4 mL, 45.2 mmol), and stirred for 21 h at room temperature. The resulting mixture was quenched with water and extracted with ether. The organic layer was washed with 3% HCl and then the combined aqueous layers were extracted with ether (×2). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (*n*-hexane:ethyl acetate = 3:1) gave 1.81 g (95%) of **10b** as a colorless oil: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.32 (br s, 1H), 4.74 (s, 2H), 4.71 (br s, 2H), 3.42 (s, 3H), 2.86 (t, J = 6.5 Hz, 2H), 2.62–2.01 (m, 4H); IR (neat) 2950, 1670, 1560, 1440, 1380, 1140, 1100, 1050, 1040, 1000 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 210 (M^+, 5), 165 (100), 150 (20), 149 (26): HRMS (EI, 30 eV) m/z 210.0900 (M^+, calcd for $C_{11}H_{14}O_4$ 210.0891).

3-(Methoxymethyoxymethyl)benzofuran-4-ol (11a). A 30-mL round-bottomed flask was charged with sodium hydride (60% dispersion in mineral oil) (59 mg, 1.47 mmol). The sodium hydride was washed with anhydrous *n*-hexane (×3) and then suspended in anhydrous THF (6 mL). To a stirred suspension was added dropwise an anhydrous THF solution (2 mL) of **10b** (207 mg, 0.98 mmol) and then methyl benzenesulfinate[15] (230 mg, 1.47 mmol) was added. The mixture was heated at 50 °C for 5 h with stirring. After dilution with water, the resulting mixture was extracted with ether (×3). The combined organic layers were washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, a crude mixture of **10c** was obtained. The pure **10c** was obtained by recrystallization from ether: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.66–7.63 (m, 2H), 7.57–7.53 (m, 3H), 7.37 (br s, 1H), [4.733 (s), 4.703 (s)] (2H), [4.68 (d, J = 1.3 Hz), 4.67 (d, J = 1.3 Hz)] (2H), 3.50–3.45 (m, 1H), 3.42 (s, 3H), 3.29–3.18 (m, 1H), 2.90–2.64 (m, 2H), 2.27–2.16 (m, 1H); IR ($CHCl_3$) 1680, 1460, 1450 cm^{-1}; LRMS (FD, $CHCl_3$) m/z (rel inten) 335 (M^+ + 1, 16), 209 (94), 208 (100).

The crude mixture of **10c** was dissolved in anhydrous benzene (6 mL) and the solution was refluxed for 1 h with stirring. The resulting mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by chromatography on silica gel (*n*-hexane/ethyl acetate = 10:1) to give 167 mg (82%) of **11a** as a colorless solid: mp 44 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 8.10 (br s, 1H, D_2O exchangeable), 7.45 (br s, 1H), 7.21 (dd, J = 7.8, 7.6 Hz, 1H), 7.04 (dd, J = 7.8, 1.2 Hz, 1H), 6.76 (dd, J = 7.6, 1.2 Hz, 1H), 4.85 (d, J = 1.2 Hz, 2H), 4.80 (s, 2H), 3.45 (s, 3H); IR ($CHCl_3$) 3300, 1580, 1490 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 208 (M^+, 23), 147 (30), 146 (100), 45 (45). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.46; H, 5.82.

3-(Hydroxymethyl)benzofuran-4-ol (11b). To a solution of **11a** (150 mg, 0.72 mmol) in methanol (10 mL) was added 36% HCl (2 drops) and the mixture was refluxed for 70 min with stirring. The resulting mixture was cooled to room temperature and then saturated $NaHCO_3$ (5 drops) was added. After removal of methanol in vacuo, the mixture was diluted with water and extracted with ethyl acetate (×2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 4:1) to give 99 mg (84%) of **11b** as a colorless solid: mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 7.37 (br s, 1H), 7.20 (dd, J = 8.2, 7.6 Hz, 1H), 7.02 (dd, J = 8.2, 1.2 Hz, 1H), 6.74 (dd, J = 7.6, 1.2 Hz, 1H), 4.87 (d, J = 1.0 Hz, 2H); IR ($CHCl_3$) 3600, 3500–3075, 1580, 1490, 1370, 1240 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 164 (M^+, 53), 146 (100), 118 (25), 89 (21). Anal. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.80; H, 5.11.

3-(Hydroxymethyl)benzofuran-4,7-dione (12). A solution of **11b** (63 mg, 0.38 mmol) in EtOH (4 mL) was cooled to 0 °C, and an ice-cooled aqueous buffer solution of freshly prepared Fremy's salt (306 mg, 1.14 mmol dissolved in 17 mL of 0.07 M KH_2PO_4 buffer) was added dropwise over 30 min with stirring at 0 °C. The reaction mixture was stirred for an additional 40 min at 0 °C. After diluting with water, the resulting mixture was extracted with ethyl acetate (×3). The combined organic layers were washed with water and brine followed by drying over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (*n*-hexane/ethyl acetate = 1:1) gave 47 mg (69%) of **12** as a brown solid: mp 100–102 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.66 (br s, 1H), 6.75 (s, 2H), 4.73 (br s, 2H), 3.20 (br s, 1H, D_2O exchangeable); IR ($CHCl_3$) 1680, 1660, 1530 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 178 (M^+, 100). Anal. Calcd for $C_9H_6O_4$: C, 60.68; H, 3.39. Found: C, 60.63; H, 3.45.

Diels–Alder Reaction of benzofuranquinone 12 with Piperylene: 3-(Hydroxymethyl)-5-methyl-5,8-dihydronaphtho[2,3-*b*]furan-4,9-dione (13) and 3-(hydroxymethyl)-8-methyl-8,9-dihydronaphtho[2,3-*b*]furan-4,9-dione (14). General Procedure for the Uncatalyzed Reaction. A solution of **12** (1 equiv) in the appropriate solvent was added piperylene (*cis–trans* mixture) (10 equiv) and stirred unitl the completion of the reaction. The resulting mixture was diluted with ethyl acetate and washed with brine followed by drying over Na_2SO_4. After removal of the solvent, chromatography on silica gel (*n*-hexane/ethyl acetate = 2:1) gave the mixture of **13** and **14** as a brown oil.

General Procedure for the Lewis acid Catalyzed Reaction. Dichloromethane was distilled from CaH_2 and then further distilled from P_2O_5, and store under molecular sieves 4A. Benzofuranquinone **12** was purified by recrystallization (ethyl acetate/*n*-hexane) and were removed containing water by azeotropic distillation with toluene before use. Piperylene (*cis–trans* mixture) was distilled under argon and stored under molecular sieves 4A.

(A) BF_3-Catalyzed Diels–Alder Reaction. A solution of **12** (30 mg, 0.17 mol) in anhydrous dichloromethane (5 mL) was cooled to −40 °C and then added freshly distilled BF_3·Et_2O. After stirring for 20 min, piperylene (0.17 mL, 0.17 mmol) was added. The reaction mixture was stirred at −40 °C until the completion of the reaction. The resulting mixture was added to water and then warmed to room temperature. The resulting mixture was extracted with ethyl acetate (×2). The combined organic layers were washed with water and brine followed by drying over Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (*n*-hexane/ethyl acetate = 2:1) gave the mixture of **13** and **14** as a brown oil.

(B) $TiCl_2(O\text{-}i\text{-}Pr)_2$-Catalyzed Diels–Alder Reaction. A suspension of **12** (30 mg, 0.17 mmol) and powdered molecular sieves 4A (300 mg) in anhydrous dichloromethane (5 mL) was cooled and added to a dichloromethane solution (0.28 mL) of $TiCl_2(O\text{-}i\text{-}Pr)_2$ which was freshly prepared from equimolar amounts of $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$.[21] After stirring for 1 h, piperylene (0.17 mL, 0.17 mmol) was added. The reaction mixture was stirred at low temperature until the completion of the reaction. By the same workup described for the BF_3·Et_2O-catalyzed reaction, the mixture of **13** and **14** was obtained. Spectral data of the mixture of **13** and **14** is as follows: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.59 (br s, 1H), 5.88–5.76 (m, 2H), [4.71 (d, J = 1.0 Hz), 4.70 (d, J = 1.2 Hz)] (2H), 3.60–2.96 (m, 4H, D_2O exchangeable to 3H), [1.24 (d, J = 2.0 Hz), 1.21 (d, J = 2.0 Hz)] (3H); IR ($CHCl_3$) 3600–3200, 3100, 1660, 1580, 1530, 1360 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 244 (M^+, 8), 242 (14), 226 (100); HRMS (EI, 30 eV) m/z 210.0900 (M^+, calcd for $C_{11}H_{14}O_4$ 210.0891).

Aromatization of 13 and 14: Maturone (15) and Isomaturone (16). In a sealed tube, the mixture of **13** and **14** (46 mg, 0.19 mmol) was dissolved in *m*-xylene (15 mL). To the reaction mixture was added chloranil (230 mg, 0.94 mmol) and it was heated for 24 h at 140 °C. After removal of the solvent in vacuo, chromatography on silica gel (*n*-hexane/ethyl acetate = 3:1) gave the mixture of maturone (**15**) and isomaturone (**16**) (36 mg, 79%) as a yellow solid. Recrystallization of the mixture of **15** and **16** from acetone/*n*-hexane afforded pure maturone as yellow needles: IR and ^{1}H NMR spectra of maturone were consistent with the spectra reported in the literature;[16,19] mp 167–168 °C (lit.[16] 169–170 °C); LRMS (EI, 30 eV) *m/z* (rel inten) 242 (M^+, 39), 224 (100), 139 (29), 57 (27). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.26; H, 4.26.

Supplementary Material Available: Copies of ^{1}H NMR spectra of **4c**, **6**, **10b**, **13/14** and **15** (8 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.