Lewis Acid Catalyzed Reaction of *o*-[1-(Alkylthio)alkyl]phenols: The Generation and Reaction of *o*-Quinonemethides and Applications to Cannabinoid Synthesis

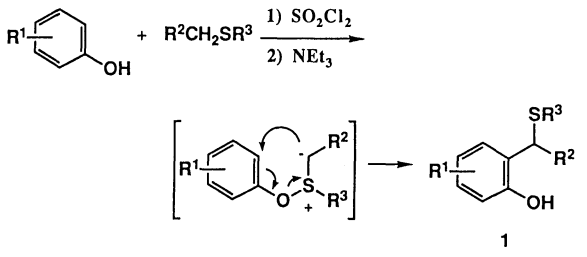
Tsutomu INOUE, Seiichi INOUE, and Kikumasa SATO*
Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Tokiwadai, Hodogaya-ku, Yokohama 240
(Received December 20, 1989)

o-Quinonemethides were prepared by treating *o*-[1-(alkylthio)alkyl]phenols with a Lewis acid. The Diels-Alder reaction of the resulting *o*-quinonemethides was also catalyzed by the Lewis acid. Hexahydrocannabinol was synthesized according to this method.

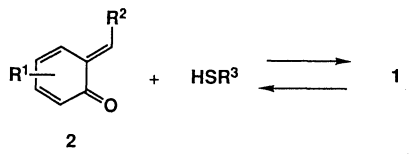
In the course of our synthetic studies of natural products,[1] an effective synthetic method of *o*-[1-(alkylthio)alkyl] phenols (**1**) via [2,3]sigmatropic rearrangement has been developed for the purpose of *ortho*-alkylation of phenols (Scheme 1).[1a-c] The usefullness of **1** was shown in the easy syntheses of phenol derivatives, for example, salicylaldehyde, coumarins,[1a] benzofurans,[1c] and benzopyrans.[1b] Moreover, noting the important roles of *o*-quinonemethides (**2**) in the synthesis of chroman, chromene, and other oxygen heterocycles, we recently reported the method to give **2** by using **1** as starting materials.[2] Since alkylthio groups on the benzyl position of **1** act as good leaving groups, these compounds can be efficiently converted from **1**.

It has been known that **2** has been used not only as heterodiene in the Diels-Alder reaction but also as the Michael acceptor.[4] Although some Michael reactions of enones with thiols are known as the reversible reaction,[5] there has been no report on the generation of **2** on the basis of the reversible reaction. The structure of **1** is the same as that of the Michael adduct between **2** and thiol. Our new generation method was achieved from this viewpoint.[3]

In this paper, we report the preparation of **2** by the treatment of **1** with a Lewis acid (Scheme 2). Also **2** is made to react with dienophiles to give chromans by the Diels-Alder reaction or with aromatics to give novel 1,3-diarylcyclohexane derivatives via a new type of Friedel-Crafts reaction. The effectiveness of this method is further demonstrated by the synthesis of cannabinol relatives.



Scheme 1.



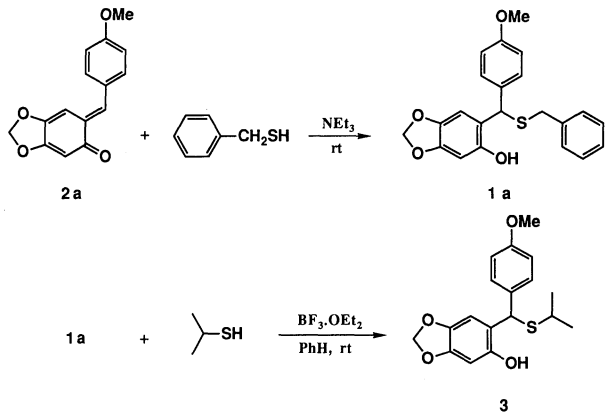
Scheme 2.

Results and Discussion

We chose (*E*)-6-(4-Methoxybenzylidene)-3,4-methylenedioxycyclohexa-2,4-dienone (**2a**),[6] which was stable in isolation, as a starting **2** for the preparation of *o*-[1-(alkylthio)alkyl]phenol (**1a**) by the Michael reaction. Treating of **2a** with phenylmethanethiol in triethylamine at room temperature gave the Michael adduct **1a** in 80% yield.

In order to examine the reverse reaction, the benzene solution of **1a** was treated with boron trifluoride etherate at room temperature. The red coloration of the solution strongly suggested the formation of **2a**. When this treatment was run in the presence of 2-propanethiol, *o*-[α-(isopropylthio)-4-methoxybenzyl]-phenol (**3**) was produced in 39% yield and **2a** was recovered in 33% yield (Scheme 3). This confirmed that **1** was equilibriumly converted to **2** in an equilibrium and thiol by the Lewis acid treatment.

The intermolecular hetero Diels-Alder reaction of **2** with electron-rich olefins has generally been carried



Scheme 3.

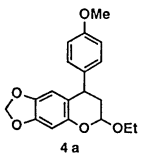
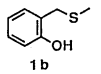
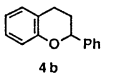
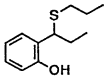
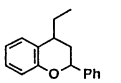
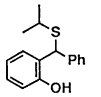
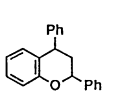
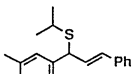
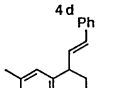
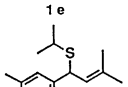
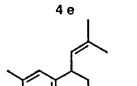
out at high temperatures,[7] although the reaction with vinyl ethers proceeds smoothly at room temperature.[2] In our present reversible reaction, **2** was thought to react with various olefins at lower temperatures to give Diels-Alder cycloadducts through activation of **2** with the Lewis acid predicted theoretically.[7,8] Actually, styrene being added in this system as a dienophile, the Diels-Alder reaction was carried out at room temperature. The results are summarized in Table 1.

By using *o*-alkyl- and *o*-benzylphenols **3** and **1b—d** as precursors of **2** the corresponding intermolecular cycloadducts **4a—d** were obtained at room temperature. When allylphenols **1e,f** were used as starting materials, **4e** and **f** were exclusively provided by the reaction of the corresponding 6-allylidenecyclohexadienone with the dienophiles without any formation of intramolecularly cyclized chromenes, which were reported to be the major products on oxidation of allylphenols via isomerization of *cis*-*o*-quinonemethides or acid-catalyzed dehydration of 1-(*o*-hydroxyphenyl)allyl alcohol via carbenium intermediates.

It is noteworthy that by the use of the present method various intermolecular Diels-Alder adducts were readily provided at room temperature.

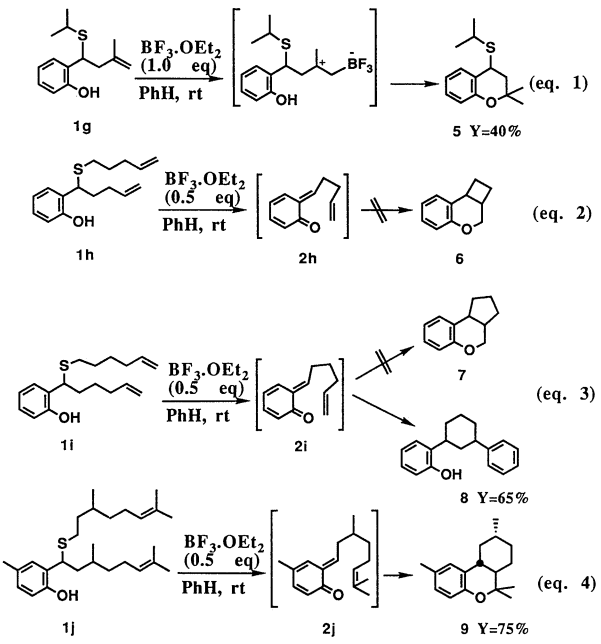
In our previous report,[1b] the treatment of a 2-[1-(alkylthio)-3-butenyl]phenol with a Lewis acid in dichloromethane afforded a 4-(alkylthio)chroman.

Table 1. Diels-Alder Reaction of *o*-Quinonemethide with Dienophile[a]

Phenol	Dienophile	$BF_3 \cdot OEt_2$ (mole equiv)	Product	(Yield%)
3		(0.05)	 4a	(90)
 1b		(3.0)	 4b	(36)
 1c		(0.50)	 4c	(50)
 1d		(0.15)	 4d	(64)
 1e		(0.05)	 4e	(69)
 1f		(0.05)	 4f	(90)

a) Carried out using **1** or **3** (1 mmol), dienophile (30 mmol), and benzene (15 ml) at room temperature.

The reaction seems to proceed not through **2** but through carbenium intermediate due to the alkylthio moiety remaining on its benzyl position. Next, the behavior of **1** possessing a double bond in the side-chain was investigated by the present method.



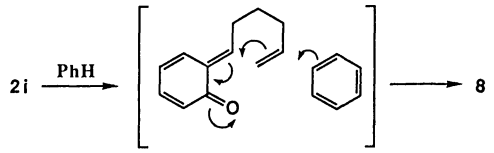
It was found that *o*-(3-butenyl)phenol (**1g**) was converted into 2,2-dimethyl-4-(isopropylthio)chroman (**5**) probably via an ionic intermediate (Eq. 1). *o*-(4-Pentenyl)phenol (**1h**) was recovered unchanged (Eq. 2). Thus, the presumed *o*-quinonemethides which might be led from **1g** or **1f** would not react with their 3- or 4-double bonds intramolecularly under the present reaction conditions.

o-(5-Hexenyl)phenol (**1i**) gave a 1,3-diarylcyclohexane derivative (**8**) in 65% yield (Eq. 3). The structure of **8** was analyzed by 400 MHz ^{1}H NMR. The decoupling measurement of two protons on the cyclohexane carbons, to which the aromatic rings were attached, did not indicate that they were coupled to each other. The existence of at least one proton, which was coupled with the two protons, was proved by COSY spectrum. These results support that the cyclohexane ring is substituted by two aromatic rings in the 1,3-position.

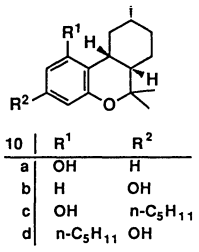
To explain the formation of **8**, we postulate the mechanism containing two consecutive electrophilic attacks; the first is the electrophilic attack of the *o*-quinonemethide upon the terminal double bond and the second is the attack of the electrophilic center, formed as the result of the first, upon the aromatic ring of the solvent (Scheme 4). The similar reaction to this was observed in the acid-catalyzed polyene epoxide cyclization.[9] Since **2h** did not afford the corresponding cyclopentane derivative, only the 6-membered transition state seemed be preferred in this reaction.

When mesitylene was used as solvent, the corresponding cyclohexane derivative was also obtained in 60% yield. This reaction could be recognized as a Friedel-Crafts reaction.

Hexahydrodibenzo[*b*,*d*]pyran (**9**),[10] which had a trans ring juncture,[11] was efficiently produced from *o*-(6-heptenyl)phenol (**1j**) as a result of the intramolecular Diels-Alder reaction via 6-membered chair-like side chain conformation (**2j**) of the transition state (Eq. 4).[12] On the other hand, the corresponding intramolecular cycloadduct, benzocyclobutapyran and benzocyclopentapyran, were not obtained from **1h** and **1i** (Eq 2,3). Since pyrolysis of 2-(1-hydoroxy-5-pentenyl)phenol gave **6** via the 5-membered conformation of the transition state (**2i**),[13] 4- and 5-membered transition states **2h** and **2i** were unfavorable to the intramolecular Diels-Alder reaction at room temperature.



Scheme 4.



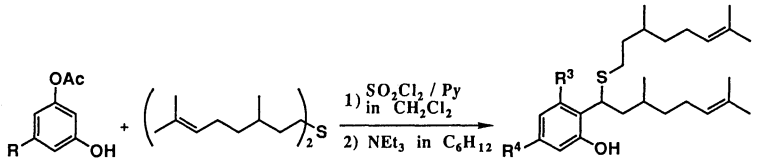
10	R^1	R^2
a	OH	H
b	H	OH
c	OH	n-C_5H_{11}
d	n-C_5H_{11}	OH

Scheme 5.

We turned our attention to the preparation of relatives of hexahydrocannabinol,[14] **10a—d**, by taking advantage of the intramolecular Diels-Alder reaction in our method (Scheme 5). The *ortho*-alkylation of 3-acetoxyphenol (**11a**) was achieved by the [2,3]-sigmatropic rearrangement of a phenoxy sulfonium ylid which was prepared from **11a** and sulfide (**12**). After silica-gel chromatography, the two regio isomers, 3-acetoxy-2-citronellylphenol (**13a**) and 5-acetoxy-2-citronellylphenol (**13b**), were isolated in 28 and 30% yields, respectively (scheme 6).

Attempted cyclization reaction of both **13a** and **13b** with $BF_3 \cdot OEt_2$ resulted in the recovery of the starting phenols. Probably, the acetoxyl group on the aromatic rings induced this result (cf. Eq. 4). Since even **13b** failed to be converted to the intramolecular Diels-Alder adduct, a steric hindrance of the group would not be thought of as a substantial interfering entity of the cyclization reaction. The problem was solved by use of 4-hydroxyphenol (**14b**), produced by the cleavage of acetoxyl group of **13b** with lithium aluminum hydride (LAH) in ether as the substrate. The treatment of **14b** with $BF_3 \cdot OEt_2$ in benzene gave the desired product **10b** in 66% yield based on **13b**. The trans ring juncture was confirmed by close agreement of the coupling constants for ^1H NMR spectra of **6a—10a** with those of **9**. According to this procedure, **10a**[11] was obtained from **13a** in 53% yield (scheme 7).

Finally, hexahydrocannabinol (HHC; **10c**) and the regio isomer (**10d**) were synthesized. The alkylation

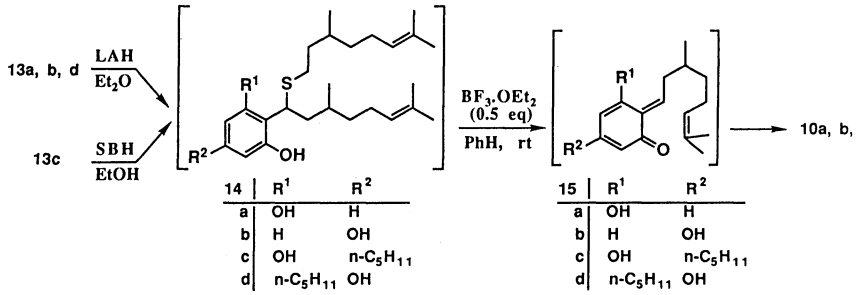


11	R
a	H
b	n-C_5H_{11}

12

13	R^3	R^4
a	OAc	H
b	H	OAc
c	OAc	n-C_5H_{11}
d	n-C_5H_{11}	OAc

Scheme 6.



14	R^1	R^2
a	OH	H
b	H	OH
c	OH	n-C_5H_{11}
d	n-C_5H_{11}	OH

15	R^1	R^2
a	OH	H
b	H	OH
c	OH	n-C_5H_{11}
d	n-C_5H_{11}	OH

Scheme 7.

of olivetol monoacetate (**11b**) with **12** was done by the [2,3]sigmatropic rearrangement to give 3-acetoxyphenol (**13c**) and 5-acetoxyphenol (**13d**) in 25 and 23% yields, respectively. **10d** was obtained by the similar method to those of **10a** and **10b** in 51% yield from **13d**. The cleavage of acetoxyl group of **13c** with sodium borohydride in ethanol at 50 °C gave a better result rather than with LAH. The treatment of hydroxyphenol (**14c**) with $BF_3 \cdot OEt_2$ in benzene afforded HHC in 71% yield from **13c**.

In conclusion, it was found that in the presence of Lewis acid there was an equilibrium between **1** and **2**. Since **2** is activated by the Lewis acid at the same time, **2** reacts with olefins in the manner of intermolecular Diels-Alder reaction at room temperature. In the case of intramolecular reaction, dibenzo[*b,d*]pyran ring system was easily and effectively obtained through the transition state possessing the 6-membered conformation of side chain, and, moreover, cyclohexane derivatives were prepared by the Friedel-Crafts reaction. HHC and its relatives were also synthesized more easily by the method than by reported methods.[11,15]

Experimental

Melting points were determined on a Shimadzu MM-2 hot-stage apparatus and were uncorrected. IR spectra were measured on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were obtained by JEOL FT-9O-Q, JEOL JNM-FX270, or JEOL GSX400 with TMS as an internal standard. Mass spectra were recorded with a HITACHI M-80 GC mass spectrometer. The column chromatography was done by use of Wakogel C-200 (Wako Pure Chemical Industries).

Michael Reaction of 2a with Phenylmethanethiol. Phenylmethanethiol (0.124 g, 1.0 mmol) was added dropwise to a solution of **2a** (0.256 g, 1.0 mmol) in triethylamine (3 ml) at room temperature. After 10 h the reaction mixture was concentrated. The crude product was chromatographed on a column with 30% EtOAc-hexane to afford 2-(α benzylthio-4-methoxybenzyl)-4,5-methylenedioxyphenol (**1a**) (0.301 g, 79%): ^{1}H NMR (90 MHz) ($CDCl_3$) δ=3.43 (2H, s, SCH_2Ph), 3.59 (3H, s, OCH_3), 4.86 (1H, s, benzyl-H), 5.62 (2H, s, OCH_2), 6.20 (1H, s, H-6), 6.32 (1H, s, OH), 6.33 (1H, s, H-3), 6.60 (2H, d, *J*=8.5 Hz, H-2′ and 6′), 6.9—7.2 (7H, m, ArH); IR(neat) ν 3400, 3050, 2900, 1610, 1510, 1480, 1250, 1040, 840, and 690 cm^{-1}. C, 69.39; H, 5.46%. Calcd for $C_{22}H_{20}O_4S$: C, 69.47; H, 5.26%.

Lewis Acid Treatment of 1a with 2-Propanethiol. Boron trifluoride etherate (0.075% (v/v) solution in benzene, 5 ml, 0.03 mmol) was added to a mixture of **1a** (0.228 g, 0.60 mmol), 2-propanethiol (0.2 ml, 2 mmol), and benzene (5 ml). The reaction mixture immediately became a red solution. Then, after stirring for 18 h at room temperature, the mixture was poured into ice water and extracted with ether (20 ml×2). The combined organic layer was washed with aq $NaHCO_3$, dried with $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on a column of silica gel with 30% CH_2Cl_2-hexane to recover **1a** (0.076 g, 33%). The last fraction from the chromatography gave **3** (0.079 g, 39%).[10]

General Procedure for the Preparation of 2-[1-(Alkylthio)alkyl]phenol 1. **1b—j** and **13a—d** were prepared by the method described in the literature.[10]

2-(1-Propylthiopropyl)phenol (1c): ^{1}H NMR (90 MHz) ($CDCl_3$) δ=0.90 (3H, t, *J*=7.6 Hz, $S(CH_2)_2C\underline{H}_3$), 0.93 (3H, t, *J*=7.3 Hz, $ArCHCH_2C\underline{H}_3$), 1.52 (2H, tq, *J*=7.1 and 7.6 Hz, $SCH_2C\underline{H}_2Me$), 1.93 (2H, dq, *J*=7.6 and 7.6 Hz, $ArCHC\underline{H}_2Me$), 2.31 (2H, t, *J*=7.1, SCH_2), 3.86 (1H, t, *J*=7.6 Hz, ArCH), 6.7—7.5 (4H, m, ArH), 7.53 (1H, s, OH); IR(neat) ν 3300, 2950, 1580, 1490, 1450, 1230, and 750 cm^{-1}.

2-[1-(5-Hexenylthio)-5-hexenyl]phenol (1i): ^{1}H NMR (90 MHz) ($CDCl_3$) δ=1.21—1.66 (6H, m, $ArCHCH_2C\underline{H}_2$ and $SCH_2C\underline{H}_2C\underline{H}_2$), 1.72—2.16 (6H, m, $ArCHC\underline{H}_2CH_2C\underline{H}_2$ and $SC_3CH_2C{=}C$), 2.32 (2H, bt, *J*=6.6 Hz, SCH_2), 3.95 (1H, t, *J*=7.3 Hz, ArCH), 4.93 (2H, d, *J*=10.0 Hz, *cis*-$\underline{H}CH{=}H$), 4.97 (2H, d, *J*=16.1 Hz, *trans*-$\underline{H}CH{=}CH$), 5.74 (2H, ddt, *J*=16.1, 10.0, and 6.6 Hz, $C\underline{H}{=}CH_2$), 6.73—7.25 (4H, m, ArH), 7.27 (1H, s, OH); IR (neat) ν 3300, 2950, 1640, 1490, 1460, 1240, 1000, 920, and 760 cm^{-1}.

3-Acetoxy-2-(1-citronellylthio-3,7-dimethyl-6-octenyl)-phenol (13a): ^{1}H NMR (90 MHz) ($CDCl_3$) δ=0.74—0.96 (6H, m, $C\underline{H}_3CH$), 1.05—2.17 (16H, m, alkyl-H), 1.57 (6H, s, *trans*-$CH_3CMe{=}C$), 1.67 (6H, s, *cis*-$CH_3CMe{=}C$), 2.29 (3H, s, $OCOCH_3$), 4.38 (1H, bt, *J*=7.6 Hz, ArCH), 5.06 (2H, bs, vinyl-H), 6.59 (1H, bd, *J*=8.1 Hz, H-6), 6.78 (1H, bd, *J*=8.1 Hz, H-4), 7.16 (1H, dd, *J*=8.1 and 8.1 Hz, H-5), 8.1 and 8.2 (1H, br, OH); IR (neat), ν 3250, 2900, 1770, 1620, 1590, 1470, 1200, and 1020 cm^{-1}.

5-Acetoxy-2-(1-citronellylthio-3,7-dimethyl-6-octenyl)-phenol (13b): ^{1}H NMR (90 MHz) ($CDCl_3$) δ=0.74—0.95 (6H, m, $C\underline{H}_3CH$), 1.05—2.15 (16H, m, alkyl-H), 1.59 (6H, s, *trans*-$CH_3CMe{=}C$), 1.68 (6H, s, *cis*-$CH_3CMe{=}C$), 2.27 (3H, s, $OCOCH_3$), 4.04 (1H, bt, *J*=6.1 Hz, ArCH), 5.06 (2H, bs, vinyl-H), 6.60 (1H, bd, *J*=7.6 Hz, H-4), 6.64 (1H, s, H-6), 6.99 (1H, d, *J*=7.57 Hz, H-3), 7.26 (1H, s, OH); IR (neat) ν 3250, 2900, 1770, 1610, 1440, 1200, and 1020 cm^{-1}.

3-Acetoxy-2-(1-citronellylthio-3,7-dimethyl-6-octenyl)-5-pentylphenol (13c): ^{1}H NMR (90 MHz) ($CDCl_3$) δ=0.77—1.05 (9H, m, $C\underline{H}_3CH$ and ArC_4CH_3), 1.0—2.4 (24H, m, alkyl-H), 1.57 (6H, s, *trans*-$CH_3CMe{=}C$), 1.66 (6H, s, *cis*-$CH_3CMe{=}C$), 2.30 (3H, s, $OCOCH_3$), 4.23 (1H, t, *J*=7.2 Hz, ArCH), 5.00 (2H, bt, *J*=7.0 Hz, vinyl-H), 6.60 (2H, s, H-4 and 6), 8.1—8.3 (1H, br, OH); IR (neat) ν 3220, 2920, 1770, 1620, 1590, 1450, 1200, and 1030 cm^{-1}.

General Procedure for Preparation of 4. Boron trifluoride etherate (3.0—0.05 mmol) was added to a mixture of **1** (1.0 mmol), styrene (30 mmol), and benzene (15 ml). After stirring for 18 h at room temperature, the mixture was poured into ice water and extracted with ether (30 ml×2). The combined organic layer was washed with aq $NaHCO_3$, dried with $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed to give chroman **4**.

***cis*-4-Ethyl-2-phenylchroman (4c):** ^{1}H NMR (400 MHz) ($CDCl_3$) δ=0.95 (3H, t, *J*=7.3 Hz, CH_3), 1.55 (1H, ddq, *J*=14.0, 8.9, and 7.3 Hz, $MeC\underline{H}HCH$), 1.79 (1H, ddd, *J*=13.4, 11.6, and 11.6 Hz, H^a-3), 2.11 (1H, ddq, *J*=14.0, 4.0, and 7.3 Hz, $MeCH\underline{H}CH$), 2.27 (1H, ddd, *J*=13.4, 5.8, and 1.8 Hz, H^e-3), 3.07 (1H, m, H-4), 5.03 (1H, dd, *J*=11.6 and 1.8 Hz, H-2), 6.91 (1H, dd *J*=7.3 and 1.5 Hz, H-8), 6.92 (1H, ddd, *J*=7.3, 7.3, and 1.5 Hz, H-6), 7.12 (1H, ddd, *J*=7.3, 7.3, and 1.5 Hz, H-7), 7.14 (1H, dd, *J*=7.3 and 1.5 Hz, H-5), 7.28—7.48 (5H, m, ArH); IR (neat) ν 2950, 1490, 1230, 750, and 700 cm^{-1}. Found: *m/z* 238.1374. Calcd for $C_{17}H_{18}O$: M, 238.1357.

***cis*-2,4-Diphenylchroman (4d):** ^{1}H NMR (270 MHz) ($CDCl_3$) δ=2.26 (1H, ddd, J=12.2, 11.9, and 11.2 Hz, H^a-3), 2.90 (1H, dd, J=12.2 and 5.6 Hz, H^e-3), 4.34 (1H, dd, J=11.9, and 5.6 Hz, H-4), 5.20 (1H, d, J=11.2 Hz, H-2), 6.77—7.49 (m, 14H, ArH); IR (neat) ν 2950, 1490, 1230, 750, and 700 cm^{-1}. Found: m/z 286.1350. Calcd for $C_{21}H_{18}O$: M, 286.1356.

***cis*-6-Methyl-2-phenyl-4-(*E*)-styrylchroman (4e):** mp 119—121 °C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ=2.05 (1H, ddd, J=13.2, 11.4, and 11.4 Hz, H^a-3), 2.22 (1H, ddd, J=13.2, 5.9, and 1.7 Hz, H^e-3), 2.23 (3H, s, CH_3), 3.86 (1H, ddd, J=11.4, 9.0, and 5.9 Hz, H-4), 5.12 (1H, dd, J=11.4 and 1.7 Hz, H-2), 6.16 (1H, dd, J=15.6 and 9.0 Hz, -CH=CPh), 6.60 (1H, d, J=15.6 Hz, -C=CHPh), 6.92 (1H, d, J=9.0 Hz, H-8), 6.98 (1H, d, J=9.0 Hz, H-7), 6.01 (1H, s, H-5), 7.2—7.5 (m, 10H); IR (KBr) ν 3020, 1490, 1230, 960, 760, and 700 cm^{-1}. Found: m/z 326.1667. Calcd for $C_{24}H_{22}O$: M, 326.1669.

***cis*-6-Methyl-4-(2-methyl-1-propenyl)-2-phenylchroman (4f):** ^{1}H NMR (400 MHz) ($CDCl_3$) δ=1.78 (3H, d J=1.2 Hz, *trans* -C=C(CH_3)Me), 1.80 (3H, d, J=1.2 Hz, *cis* -C=C(CH_3)Me), 1.87 (1H, ddd, J=13.7, 11.9, and 11.9 Hz, H^a-3), 2.12 (1H, ddd, J=13.7, 5.7, and 1.8 Hz, H^e-3), 2.26 (3H, s, $ArCH_3$), 3.92 (1H, ddd, J=11.9, 9.5, and 5.1 Hz, H-4), 5.07 (1H, dd, J=11.9 and 1.8 Hz, H-2), 5.08 (1H, ddd, J=9.5, 1.2, and 1.2 Hz, vinyl-H), 6.79 (1H, d, J=8.2 Hz, H-8), 6.89 (1H, s, H-5), 6.92 (1H, d, J=8.2 Hz, H-7), 7.3—7.5 (5H, m, ArH); IR (neat) ν 2900, 1490, 1240, 900, and 820 cm^{-1}. Found: m/z 278.1699. Calcd for $C_{20}H_{22}O$: M, 278.1699.

2-(3-Phenylcyclohexyl)phenol (8). To a solution of **1i** (0.290 g, 1.0 mmol) in benzene (15 ml) was added boron trifluoride etherate (0.5 mmol). After stirring for 18 h at room temperature, the mixture was poured into ice water and extracted with ether (30 ml×2). The combined organic layer was washed with aq $NaHCO_3$, dried with $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed to give 0.164 g of **8** (65% yield): ^{1}H NMR (400 MHz) ($CDCl_3$) δ=1.49 (2H, dq, J=12.2 Hz, H-5′), 1.62 (2H, dq, J=12.2 Hz, H^a-4′ and H^a-6′), 1.97 (3H, bt, J=11.2 Hz, H^a-2′, H^e-4, and H^e-6′), 2.07 (1H, bd, J=12.5 Hz, H^e-2′), 2.74 (1H, bt, J=12.0 Hz, H^a-3′), 3.05 (1H, bt, J=12.0 Hz, H^a-1′), 4.82 (1H, s, OH), 6.69 (1H, d, J=7.9 Hz, H-6), 6.89 (1H, dd, J=7.9 and 7.9 Hz, H-4), 7.04 (1H, dd, J=7.9 and 7.9 Hz, H-5), 7.1—7.3 (6H, m, H-3 and Ph); IR (neat) ν 3500, 2930, 1600, 1500, 1450, 1240, 750, and 700 cm^{-1}. Found: m/z 252.1519. Calcd for $C_{18}H_{20}O$: M, 252.1524.

General Procedure for the Preparation of Hexahydrodibenzo[*b,d*]pyran (10a, 10b, and 10d). To a solution of **13** (0.20 mmol) in 10 ml of ether was added lithium aluminum hydride (0.010 g, 0.26 mmol). After being stirred for 1 h at room temperature, the reaction mixture was carefully diluted with 30 ml of water-saturated ether, then diluted with cold water (30 ml), and the mixture was filtered through Celite. The organic layer was separated and washed with cold water (20 ml). The aqueous layer was extracted with ether (10 ml×2), and the combined organic layer was dried over $MgSO_4$. As soon as the solvent was removed in vacuo, benzene (15 ml) was added to the crude product **17**. To the benzene solution was added boron trifluoride etherate (0.10 mmol). Then, after stirring for 2 h at room temperature, the mixture was poured into ice water and extracted with ether (30 ml×2). The combined organic layer was washed with aq $NaHCO_3$, dried with $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed to give **10**.

3-Hydroxy-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran (10b): mp 138—140 °C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ=0.87 (1H, bq, J=12.5 Hz, H^a-10), 0.98 (3H, d, J=6.6 Hz, CH_3-9), 1.05 (1H, bt, J=10.5 Hz, H^a-8 or H^e-8), 1.07—1.10 (1H, m, H^a-7 or H^e-7), 1.13 (3H, s, CH_3-6), 1.34 (1H, ddd, J=11.3, 11.3, and 2.9 Hz, H-6a), 1.37 (3H, s, CH_3-6), 1.57 (1H, m, H-9), 1.8—1.9 (2H, m, H^a or H^e-7 and H^a or H^e-8), 2.37 (2H, m, H-10a and H^e-10), 4.70 (1H, s, OH), 6.25 (1H, dd, J=7.6 and 2.4, H-4), 6.35 (1H, dd, J=7.6 and 2.4 Hz, H-2), 7.05 (1H, d, J=7.6 Hz, H-1); IR (KBr) ν 3200, 2950, 1620, 1590, 1500, 1450, 1140, 990, and 850 cm^{-1}. Found (acetate): m/z 288.1727. Calcd for $C_{18}H_{24}O_3$: M, 288.1724.

3-Hydroxy-1-pentyl-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran (10d): ^{1}H NMR (400 MHz) ($CDCl_3$) δ=0.84 (1H, bq, J=13.1 Hz, H^a-10), 0.90 (3H, t, J=6.7 Hz, ArC_4CH_3), 0.94 (3H, d, J=6.7 Hz, CH_3-9), 1.02 (3H, s, CH_3-6), 1.10 (1H, bpent, J=12.2 Hz, H^a-8 or H^e-8), 1.3—1.4 (5H, m, H^a-7 or H^e-7, $MeCH_2CH_2$), 1.39 (3H, s, CH_3-6), 1.48 (1H, ddd, J=11.0, 11.0, and 2.1 Hz, H-6a), 1.5—1.7 (3H, m, H-9 and $ArCH_2C\underline{H}_2$), 1.8—1.9 (2H, m, H^a or H^e-7 and H^a or H^e-8), 2.32 (1H, bd, J=13.1 Hz, H^e-10), 2.39 (1H, ddd, J=11.0, 11.0, and 2.4 Hz, H-10a), 2.54 (2H, t, J=8.1 Hz, $ArCH_2$), 4.77 (1H, s, OH), 6.12 (1H, d, J=2.4, H-4), 6.27 (1H, d, J=2.4 Hz, H-2); IR (neat) ν 3350, 2900, 1610, 1590, 1440, 1140, and 1020 cm^{-1}. Found: m/z 316.2409. Calcd for $C_{21}H_{32}O_2$: M, 288.1724.

3-Hydroxy-5-pentyl-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran (HHC; 10c). To a solution of **13c** (0.106 g, 0.20 mmol) in 2 ml of ether was added sodium borohydride (0.010 g, 0.26 mmol). After being stirred for 18h at 50 °C, the reaction mixture was cautiously diluted with 10 ml of benzene and 20 ml of water. The organic layer was separated and washed with cold water (20 ml). The aqueous layer was extracted with benzene (10 ml×2), and the combined organic layer was dried over $MgSO_4$. $MgSO_4$ was filtered, and to the benzene filtrate was added boron trifluoride etherate (0.10 mmol). Then, after stirring for 2 h at room temperature, the mixture was poured into ice water and extracted with ether (30 ml×2). The combined organic layer was washed with aq $NaHCO_3$, dried with $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed to give 0.045 g of HHC[15a] (71% yield): ^{1}H NMR (270 MHz) ($CDCl_3$) δ=0.78 (1H, bq, J=13.1 Hz, H^a-10), 0.88 (3H, t, J=6.7 Hz, ArC_4CH_3), 0.94 (3H, d, J=6.7 Hz, CH_3-9), 1.07 (3H, s, CH_3-6), 1.10 (1H, m, H^a-8 or H^e8), 1.36 (3H, s, CH_3-6), 1.2—1.5 (6H, m, H^a or H^e-7, H-6a, and $MeC\underline{H}_2C\underline{H}_2$), 1.5—1.7 (3H, m, H-9 and $ArCH_2\underline{H}_2$), 1.8—1.9 (2H, m, H^a or H^e-7 and H^a- or H^e-8), 2.45 (2H, t, J=6.3 Hz, $ArCH_2$), 2.47 (1H, m, H-10a), 3.10 (1H, dm, J=11.7 Hz, H^e-10), 4.71 (1H, s, OH), 6.07 (1H, d, J=1.7, H-2), 6.24 (1H, d, J=1.7 Hz, H-4); IR (neat) ν 3350, 2900, 1610, 1590, 1440, 1140, and 1020 cm^{-1}.

We would like to thank the staffs of Odawara Research Center of Nippon Soda Co., Ltd. for measuring mass and 400 MHz NMR spectra. We are also indebted to Miss Naomi Makino and Mr. Tomoyuki Kawabata for valuable technical assistance.

The present work was supported by a Grant-in-Aid for Scientific Research (Nos. 63540387 and 01540452) from the Ministry of Education, Science and Culture.

References

1) a) K. Sato, S. Inoue, K. Ozawa, T. Kobayashi, T. Ota, and M. Tazaki, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1753; b) S. Inoue, H. Ikeda, S. Sato, K. Horie, T. Ota, O. Miyamoto, and K. Sato, *J. Org. Chem.*, **52**, 5495 (1987); c) T. Ota, S. Hasegawa, S. Inoue, and K. Sato, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 3029; d) S. Inoue, N. Iwase, O. Miyamoto, and K. Sato, *Chem. Lett.*, **1986**, 2035; e) S. Inoue, N. Iwase, O. Miyamoto, and K. Sato, "Flavors and Fragrances: A World Perspective," ed by B. M. Lawrence, B. D. Mookherjee, and B. J. Willis, Elsevier, Amsterdam (1988), Developments in Food Science 18, pp. 855—866.

2) T. Inoue, S. Inoue, and K. Sato, *Chem. Lett.*, **1989**, 653.

3) A part of the results have been preliminarily presented: T. Inoue, S. Inoue, and K. Sato, *Chem. Lett.*, **1990**, 55.

4) D. A. Bolon, *J. Org. Chem.*, **35**, 715 (1970).

5) C. F. H. Allen and W. J. Humphlett, *Can. J. Chem.*, **44**, 2315 (1966).

6) L. Jurd, *Tetrahedron*, **33**, 163 (1977).

7) G. Desimoni and G. Tacconi, *Chem. Rev.*, **75**, 651 (1975).

8) P. Lanteri, R. Longeray, and J. Royer, *J. Chem. Research (S)*, **1981**, 168.

9) K. B. Sharpless, *J. Am. Chem. Soc.*, **92**, 6999 (1970); E. E. Tamelen and R. J. Anderson, *ibid.*, **94**, 8225 (1972).

10) T. Inoue, S. Inoue, and K. Sato, *Bull. Chem. Soc. Jpn.*, in press.

11) J. J. Talley, *J. Org. Chem.*, **50**, 1695 (1985).

12) L.-F. Tietze and G. v. Kiedrowski, *Tetrahedron Lett.*, **23**, 219 (1981).

13) R. Hug, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta.*, **55**, 1675 (1972); Y. Mao and V. Boekelheide, *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 1732 (1980).

14) R. Mechoulam, N. Lander, T. H. Varkony, I. Kimmel, O. Becker, Z. Ben-Zvi, H. Edery, and G. Porath, *J. Med. Chem.*, **23**, 1068 (1980).

15) a) L.-F. Tietze, G. v. Kiedrowski, and B. Berger, *Angew. Chem., Int. Ed. Engl.*, **21**, 221 (1982); b) J. P. Marino and S. L. Dax, *J. Org. Chem.*, **49**, 3671 (1984).