Direct Construction of the Chroman Structure from 1,3-Diene. Regioselective Protonation of Acyclic Polyene

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The regioselective protonation of acyclic polyene was achieved, dependent on the choice of catalyst. The addition of myrcene to trimethylhydroquinone, using boron trifluoride–diethyl ether (1/1), predominantly gave a spiro structure. When (+)-10-camphorsulfonic acid was used as a catalyst, the major compound produced was chroman.

Since the Friedel–Crafts alkylation of hydroquinones with 1,3-dienes is an important process for the synthesis of a chroman ring structure,[1] it is directly related to the syntesis of vitamin E and related compounds.[2] Despite investigations of this reaction over the years, no generally applicable catalytic system has yet been found.

Synthesis is considered to proceed through the selective protonation of 1,3-diene following Friedel–Crafts alkylation by cyclization to generate a chroman structure (Scheme 1). If so, regioselective protonation of 1, 3-diene would be a key step in this synthetic scheme. If there is an extra double bond in the system, the regiochemical problem would be even more complicated.[1a]

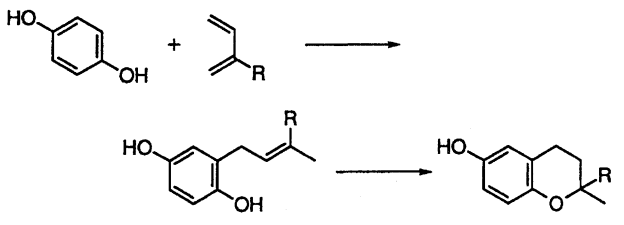
A careful investigation was made using myrcene and trimethylhydroquinone as the substrates. Protonation of myrcene can formally generate six possible carbenium ions; however, only three of these (**1**, **2** and **3**) would preferentially be formed, because of their relative stability (Scheme 2). Two of these (**2** and **3**) can form a chroman ring system. We wish to report herein that the regioselectivity of the protonation of myrcene can be controlled by the choice of a Lewis or Brønsted acid.

Results and Discussion

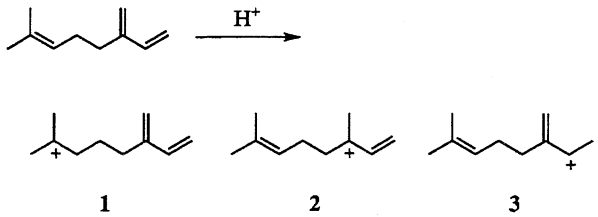
The addition of boron trifluoride–diethyl ether (1/1) to a mixture of myrcene and trimethylhydroquinone gave, after purification by column chromatography on silica-gel, the spiro compound **5** almost exclusively. The reaction clearly proceeded through the intermediary ion **1**, followed by cyclization to **4**, Friedel–Crafts alkylation and then, finally, cyclization to generate a spiro structure (Scheme 3). Similar results were also obtained using a variety of Lewis acids; the results are summarized in Table 1.

Using $BF_3 \cdot Et_2O$, the reaction proceeded smoothly to give **5** predominantly in good yields, regardless of the solvents. A GLC analysis of the products showed two major peaks of the spiro compound **5** and chroman **6** along with some minor peaks.[3] $SnCl_4$ was also an effective catalyst for selective protonation, giving the spiro compound **5** (Entry 5). The use of $TiCl_4$, $FeCl_3$, MgI_2, $ZnCl_2$, and $SbCl_5$ gave only trace amounts of the desired addition products along with a recovery of the starting trimethylhydroquinone. $Y(OTf)_3$ and $Sm(OTf)_3$, $Eu(OTf)_3$, lanthanide Lewis acid catalysts,[4] caused the addition reaction to proceed with relatively low selectivity. The formation of chroman compound **6** is rationalized as shown in Scheme 4. Initial protonation at the terminal sp^2 carbon of methylene group generated the carbenium ion **2**; then, Friedel–Crafts alkylation followed by cyclization gave the chroman compound **6**.

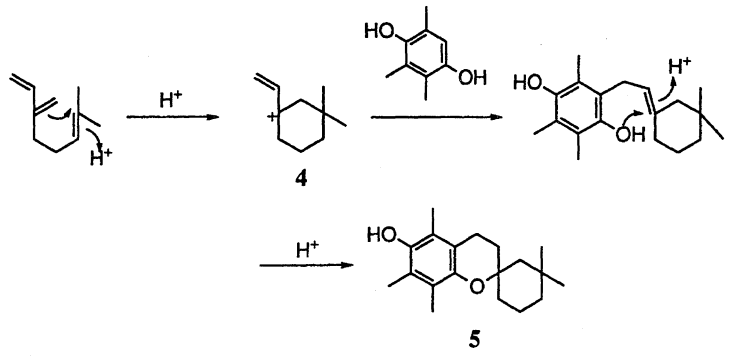
$BF_3 \cdot Et_2O$ or $SnCl_4$ as a Lewis acid catalyst possibly coordinates phenolic oxygen of trimethylhydroquinone; the resulting highly acidic proton **7** coordinates the nonconjugated monoolefin, which has a higher nucleophilic-



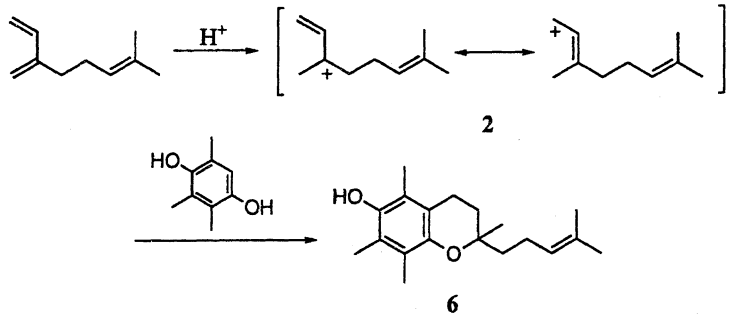
Scheme 1.



Scheme 2.

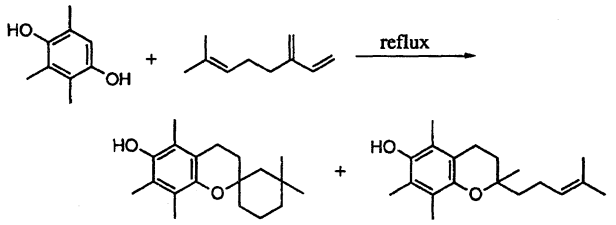


Scheme 3.



Scheme 4.

Table 1. Reactions of Trimethylhydroquinone and Myrcene Using Lewis Acids



Entry	Catalyst (molar amount)	Solvent	Time h	Product % yield[a]	Product 5 : 6[b]
1	BF_3·Et_2O (0.2)	*o*-Xylene	0.5	86	78 : 16
2	BF_3·Et_2O (1.0)	Bu_2O	3	95	78 : 13
3	BF_3·Et_2O (1.0)	*i*-Pr_2O	3	87	87 : 8
4	BF_3·Et_2O (1.0)	CH_3NO_2	3	94	76 : <1
5	$SnCl_4$ (1.0)	*o*-Xylene	3	99	80 : 2
6	$TiCl_4$ (1.0)	*o*-Xylene	3	<1	
7	$FeCl_3$ (1.0)	*o*-Xylene	3	7	53 : 24
8	MgI_2 (1.0)	*o*-Xylene	3	<1	
9	$ZnCl_2$ (1.0)	*o*-Xylene	3	10	43 : 28
10	$SbCl_5$ (0.2)	Octane	3	<1	
11	$Sm(OTf)_3$ (0.2)	Octane	3	13	43 : 36
12	$Eu(OTf)_3$ (0.2)	Octane	3	75	28 : 38
13	$Y(OTf)_3$ (0.2)	Octane	3	10	33 : 40

a) % yield of volatile product. b) Determined by GLC analysis.

ity than does conjugate diene, thereby generating a stable carbenium ion **1** (Fig. 1). Cyclization to generate a more stable carbenium ion **4** leads to Friedel–Crafts alkylation to give spiro compound **5**. Therefore, for the selective preparation of **6**, protonation should occur at conjugate diene of myrcene, which may be sterically less hindered than the substituted olefin.

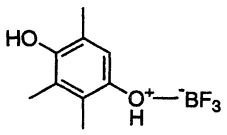


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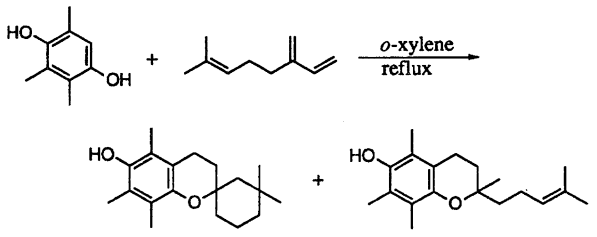
Fig. 1.

A variety of Brønsted acid catalysts were then examined; the results are given in Table 2.

The use of ion exchange resins (Amberlist 15 or Dowex-50w-X4) gave a mixture of products containing spiro compound **5** as a major product (Entries 1, 2). A heteropoly acid, such as silicomolybdic acid, produced **6** and **5** in almost the same amounts (Entry 3). Sulfonic acid gave meaningful different results from Lewis acids or solid acid catalysts. *p*-Toluenesulfonic acids gave a 15 : 29 mixture of **5**/**6** in 92% yield (Entry 4). Although the introduction of either methyl or a more bulky substituent at the benzene ring resulted in a decrease in the yield, a dramatic increase in the ratio of **6** in the volatile mixture was realized (Entries 4, 5, and 6). (+)-10-Camphorsulfonic acid (CSA) was found to be the best catalyst among the sulfonic acids to provide **6** as a rich mixture (6 : 52=**5** : **6**) in 51% yield (Entry 7). It is likely that CSA is sufficiently bulky for protonation to conjugated diene.

Based on the success of selective protonation of myrcene, the chroman ring construction from 7,11,15-

Table 2. Reactions of Trimethylhydroquinone and Myrcene Using Brønsted Acids



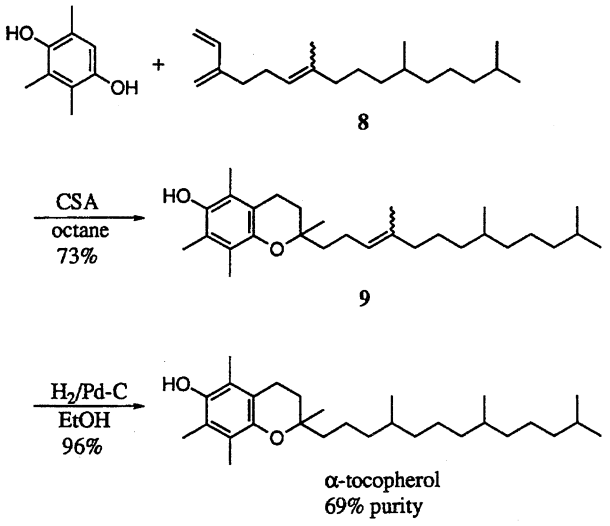
5 6

Entry	Catalyst (molar amount)	Time	Product	
		h	% yield[a]	5 : 6[b]
1	Amberlyst 15 (100 wt%)	3	75	28 : <1
2	Dowex-50W-X4 (100 wt%)	3	35	48 : 18
3	Silicomolybdic acid (0.1)	3	23	32 : 40
4	*p*-Toluenesulfonic acid (0.1)	3	92	15 : 29
5	Mesitylenesulfonic acid (0.1)	1	58	12 : 48
6	2,4,6-Triisopropylbenzenesulfonic acid (0.1)	3	45	11 : 52
7	(+)-10-Camphorsulfonic acid (0.1)	3	51	6 : 52

a) % yield of volatile product. b) Determined by GLC analysis.

trimethyl-3-methylene-1,6-hexadecadiene **8**[5] with trimethylhydroquinone was examined for the synthesis of α-tocopherol (Scheme 5). A treatment of **8** and trimethylhydroquinone in the presence of CSA under reflux in octane gave the desired 3′,4′-didehydro-α-tocopherol **9** (73%), which was converted to α-tocopherol by hydrogenation (96% yield, 69% purity). Thus, CSA was proven to be an effective catalyst for the initial regioselective protonation of polyene in the synthesis of α-tocopherol.

In summary, the selective protonation to polyenes was achieved by a correct choice of the catalyst, and selective addition reactions of the polyenes to trimethylhydroquinone to give the chroman compounds were realized. A further investigation to develop this addition reaction is now in progress.



Scheme 5.

Experimental

General. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. Analytical gas-liquid-phase chromatography (GLC) was performed on a Gaskuro Kogyo Model 370 instrument with a flame-ionization detector and a capillary column of HP-1(25m) using nitrogen as the carrier gas. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini-200 (200 MHz), Gemini-300 (300 MHz) and VXR 500S (500 MHz) spectrometer. The chemical shifts of ^{1}H NMR were reported relative to tetramethylsilane (δ=0) or chloroform (δ=7.26). The chemical shifts of ^{13}C NMR were reported relative to $CDCl_3$ (δ=77.00). The splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra were recorded on a Shimadzu QP-5000 mass spectrometer. High-performance liquid chromatography (HPLC) was performed with a JASCO UVIDEC-100-II instrument using a 4.6-mm×25-cm JASCO Finepak Sil column. All of the experiments were carried out under an atmosphere of dry argon. For the thin-layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica-gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica-gel E. Merck Art. 9385. Microanalyses were accomplished at the Faculty of Agriculture, Nagoya University.

In experiments requiring dry solvents, diethyl ether and tetrahydrofuran (THF) were purchased from Aldrich Chemical Co., Inc., and used without further purification. Benzene, toluene, and *o*-xylene were dried over sodium metal. Dichloromethane and nitromethane were stored over 4-Å molecular sieves. Myrcene was used after distillation (>90% purity). Other simple chemicals were purchased and used without further purification.

Procedure for an Addition Reaction of Myrcene to Trimethylhydroquinone Using Boron Trifluoride–Diethyl Ether (1/1) (Table 1, Entry 1): To a suspension of trimethylhydroquinone (4.0 g, 26 mmol) in *o*-xylene (20 ml) was added myrcene (9.6 ml, 93% purity,

53 mmol); the mixture was then heated under reflux for 10 min. Subsequently, boron trifluoride–diethyl ether (1/1) (0.65 ml, 5.3 mmol) was added dropwise to the solution, and the mixture was heated under reflux for 30 min. After cooling, the mixture was poured into 1 M aqueous hydrochloric acid (20 ml, 1 M=1 mol dm^{-3}) and the organic material was extracted with ethyl acetate (20 ml). After the combined organic layer was washed twice with 1 M aqueous hydrochloric acid (2×20 ml), it was washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated in vacuo. Nonpolar hydrocarbon and unreacted trimethylhydroquinone in the crude oil were separated by column chromatography on silica-gel (eluent: hexane–EtOAc) to give an addition mixture as a brown oil (6.5 g, 86% yield). The **5/6** ratio was determined to be 78/16 by GLC analysis.

Typical Procedure for Addition Reaction of Myrcene to Trimethylhydroquinone Using Lewis Acid: To a suspension of trimethylhydroquinone (0.20 g, 1.3 mmol) in *o*-xylene (6.0 ml) was added $SnCl_4$ (1.3 ml of a 1.0 M solution in dichloromethane, 1.3 mmol) at 100 °C. After being stirred for 10 min, myrcene (0.50 ml, 90% purity, 2.6 mmol) was added dropwise to the suspension with refluxing; the mixture was then heated under reflux for 3 h. After cooling, the resulting mixture was poured into 1 M aqueous hydrochloric acid (10 ml), and the product was extracted with diethyl ether (6.0 ml). The organic layer was washed with brine (10 ml), dried over anhydrous magnesium sulfate and concentrated in vacuo. Hexane (6.0 ml) was added to the crude mixture and the unreacted solid trimethylhydroquinone was filtered out. Nonpolar hydrocarbon and unreacted trimethylhydroquinone in the crude oil were separated by column chromatography on silica-gel (eluent: hexane–EtOAc) to give an addition mixture as a brown oil (0.38 g, 99% yield). The **5/6** ratio was determined to be 80/2 by GLC analysis.

Typical Procedure for Addition Reaction of Myrcene to Trimethylhydroquinone Using Ion Exchange Resin: To a suspension of trimethylhydroquinone (0.20 g, 1.3 mmol) in *o*-xylene (6.0 ml) was added Amberlyst 15 (0.20 g); the mixture was then heated at reflux for 10 min. After myrcene (0.48 ml, 93% purity, 2.6 mmol) was added dropwise to the suspension, the mixture was heated under reflux for 3 h. Then, after cooling, hexane (6.0 ml) was added to the crude mixture and the unreacted solid trimethylhydroquinone and ion exchange resin were filtered out. Nonpolar hydrocarbon and unreacted trimethylhydroquinone in the crude oil was separated by column chromatography on silica-gel (eluent: hexane–EtOAc) to give an addition mixture as a brown oil (0.29 g, 75% yield). The **5/6** ratio was determined to be >28/1 by GLC analysis.

Typical Procedure for Addition Reaction of Myrcene to Trimethylhydroquinone Using Brønsted Acid: To a suspension of trimethylhydroquinone (0.20 g, 1.3 mmol) in *o*-xylene (3.0 ml) was added (+)-10-camphorsulfonic acid (31 mg, 0.13 mmol); the mixture was heated under reflux for 10 min. Myrcene (0.48 ml, 93% purity, 2.6 mmol) was added dropwise to the suspension with refluxing, and the mixture was heated under reflux for 3 h. After cooling, the mixture was poured into saturated aqueous sodium hydrogencarbonate (10 ml) and the product was extracted with diethyl ether (6.0 ml). The combined organic layer was washed twice with saturated aqueous sodium hydrogencarbonate (2×10 ml), and then was washed with brine (10 ml), dried over anhydrous magnesium sulfate and concentrated in vacuo. Hexane (6.0 ml) was added to the crude mixture and the unreacted solid trimethylhydroquinone was filtered out. Nonpolar hydrocarbon and unreacted trimethylhydroquinone in the crude oil was separated by column chromatography on silica-gel (eluent: hexane–EtOAc) to give a addition mixture as a brown oil (0.19 g, 51% yield). The **5/6** ratio was determined to be 6/52 by GLC analysis.

3,4-Dihydro-3′,3′,5,7,8-pentamethylspiro[2*H*-1-benzopyran-2,1′-cyclohexan]-6-ol (5). IR ($CHCl_3$) 3600—3200, 2946, 1456, 1260, 1183, 1086, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=0.89 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.15 (d, 1H, J=14.0 Hz, C*H*H), 1.18 (d, 1H, J=15.0 Hz, C*H*H), 1.19 (dd, 1H, J=12.5, 3.5 Hz, C*H*H), 1.43 (m, 1H, C*H*H), 1.47 (br d, 1H, J=12.5 Hz, C*H*H), 1.66 (dt, 1H, J=13.3, 7.0 Hz, C*H*H), 1.68 (br d, 1H, J=14.0 Hz, C*H*H), 1.73 (dt, 1H, J=13.3, 7.0 Hz, C*H*H), 1.80 (m, 1H, C*H*H), 1.85 (br d, 1H, J=15.0 Hz, C*H*H), 2.11 (s, 3H, CH_3), 2.16 (s, 6H, $2CH_3$), 2.60 (t, 2H, J=7.0 Hz, CH_2), 4.19 (s, 1H, OH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ=11.3, 12.3, 12.5, 18.5, 20.4, 26.8, 30.4, 34.1, 34.3, 34.6, 39.5, 46.9, 73.9, 117.3, 118.5, 121.1, 122.5, 144.4, 145.4; MS (FAB) m/z 288 (M^+), 203, 177, 165, 149, 109, 95. Found: C, 79.01; H, 9.96%. Calcd for $C_{19}H_{28}O_2$: C, 79.13; H, 9.78%.

3,4-Dihydro-2,5,7,8-tetramethyl-2-(4-methyl-3-pentenyl)-2*H*-1-benzopyran-6-ol (6). IR ($CHCl_3$) 4000—3500, 3007, 1456, 1379, 1261, 1225, 1206, 1167, 1086 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.22 (s, 3H, CH_3), 1.54 (m, 2H, CH_2), 1.57 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.77 (m, 2H, CH_2), 2.07 (m, 2H, CH_2), 2.09 (s, 6H, $2CH_3$), 2.14 (s, 3H, CH_3), 2.59 (t, 2H, J=6.8 Hz, CH_2), 4.16 (s, 1H, OH), 5.09 (t, 1H, J=7.2 Hz, CH); MS (EI, 70eV) m/z 288 (M^+), 203, 191, 177, 165, 152, 136, 121, 69, 43. Found: C, 79.07; H, 9.87%. Calcd for $C_{19}H_{28}O_2$: C, 79.13; H, 9.78%.

Procedure for an Addition Reaction of 7,11,15-Trimethyl-3-methylene-1,6-hexadecadiene to Trimethylhydroquinone Using CSA: To a suspension of trimethylhydroquinone (0.40 g, 2.6 mmol) in octane (1.0 ml) was added (+)-10-camphorsulfonic acid (61 mg, 0.26 mmol) and 7,11,15-trimethyl-3-methylene-1,6-hexadecadiene (0.93 g, 86% purity, 2.9 mmol); the mixture was then heated under reflux for 3 h. Then after cooling, the resulting mixture was poured into saturated aqueous sodium bicarbonate (10 ml) and the product was extracted with EtOAc (6.0 ml). The combined organic layer was washed twice with saturated aqueous sodium bicarbonate (2×10 ml), and then was washed with brine (10 ml), dried over anhydrous magnesium sulfate and concentrated in vacuo. After hexane (6.0 ml) was added to the crude mixture, the unreacted solid trimethylhydroquinone was filtered out. Nonpolar hydrocarbon and unreacted trimethylhydroquinone in the crude oil was separated by column chromatography on silica-gel (eluent: hexane–EtOAc) to give an addition mixture as a brown oil (0.82 g, 73% yield).

α-Tocopherol. A mixture of the addition products (0.2 g) and 10% Pd/C (50 mg) in ethanol (10 ml) was stirred at room temperature for 12 h under H_2 gas. The reaction mixture was filtrated, and the catalyst was washed with ether. The organic layer was concentrated in vacuo. The crude oil was purified by column chromatography on silica-gel (eluent: hexane–EtOAc) to give α-tocopherol as a yellow brown oil

(0.19 g, 96% yield). The purity was determined to be 69% by GLC analysis.

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2) C. G. Cardenas and Z. U. Din, U. S. Patent 4168271 (1979).

3) Authentic **5** and **6** were prepared by the literature procedure, see: a) Ref. 1a; b) T. Ichikawa, *Bull. Chem. Soc. Jpn.*, **41**, 1224 (1968).

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5) Synthesis of 7,11,15-trimethyl-3-methylene-1,6-hexadecadiene (**8**) has been established. See: a) K. Hamamura, Y. Ohkuni, Y. Narabe, Y. Hisatake, T. Banba, and S. Kijima, JP Patent 89215736 (1989); b) K. Hamamura, Y. Ohkuni, Y. Narabe, Y. Hisatake, T. Banba, and S. Kijima, JP Patent 89285633 (1989); c) Ref. 2. The compound **8** was kindly donated by Eisai Co., Ltd., Tokyo.