Convenient Synthesis of Biphenyl-2-carboxylic Acids via the Nucleophilic Aromatic Substitution Reaction of 2-Methoxybenzoates by Aryl Grignard Reagents[1)]

Tetsutaro HATTORI, Takatsugu SUZUKI, Noriyuki HAYASHIZAKA,† Nobuyuki KOIKE, and Sotaro MIYANO*
Department of Biochemistry and Engineering, Faculty of Engineering, Tohoku University, Aramaki-Aoba, Aoba-ku, Sendai 980
†Sumitomo Seika Chemicals Co., Ltd., 346-1, Miyanishi, Harima-cho, Kako-gun, Hyogo 675-01
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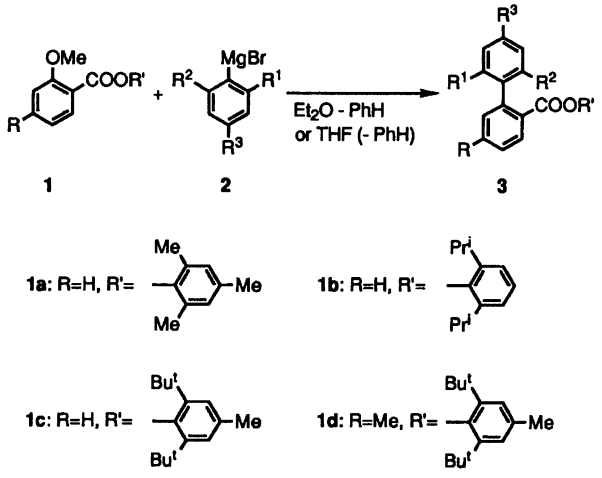
Nucleophilic aromatic substitution (S_NAr) of 2-methoxybenzoic esters derived from 2,6-dialkylphenols by aryl Grignard reagents affords 1,1′-biphenyl-2-carboxylates in excellent yields by proper choice of the bulk of the 2,6-dialkyl-substituents. The phenoxyl protecting groups can be easily removed from the resulting biphenyl-2-carboxylates to the free acids by treatment with potassium hydroxide in aqueous ethanol (2,4,6-trimethylphenyl and 2,6-diisopropylphenyl esters) or sodium methoxide in toluene–hexamethylphosphoric triamide (2,6-di-*t*-butyl-4-methylphenyl esters). The regioselective biphenyl coupling reaction via the S_NAr process is utilized for the key-step construction of the biphenyl skeleton in a formal synthesis of cannabinol.

The biphenyl framework constitutes one of the structural features in a number of natural products[2)] and high-performance molecules such as liquid crystals[3)] and chiral auxiliaries,[4)] and thus the construction of the biphenyl structure continues to be an important problem in synthetic organic chemistry.[5)] In this context, preparation of biphenyl-2-carboxylic acids is of particular importance because those are crucial intermediates, via the manipulations of the carboxyl group, to several naturally occurring, biologically active biphenyls, dibenzopyranones, and fluorenones and the like.[6)] Among recent various routes to the bipheyl-2-carboxylic derivatives,[7)] the versatility of the Meyers reaction is eminent.[8,9)] In this transformation, the carboxyl group of 2-methoxybenzoic acids is converted into an oxazoline, which serves both as a protecting group and an activating group for nucleophilic aromatic substitution (S_NAr) of the 2-methoxyl group by aryl Grignard reagents to afford the 2-oxazoline-substituted biphenyls. Hydrolysis of the latter furnishes the biphenyl-2-carboxylic acids. In a preliminary communication,[1)] we reported an improved variant of the Meyers reaction where the oxazoline functionality can be replaced by readily preparable and removable 2,6-dialkyl-substituted phenoxycarbonyl substituents (Scheme 1). As a follow-up to the communication, herein we describe in detail a very practical method for the synthesis of biphenyl-2-carboxylic acids via the reaction of 2,6-dialkylphenyl 2-methoxybenzoates **1** with aryl Grignard reagents **2**.

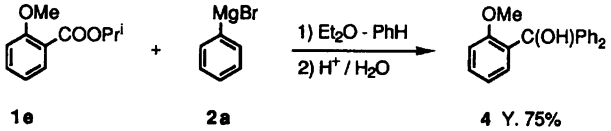
Results and Discussion

Control of the Grignard Addition to the Ester Carbonyl Group of the 2-Methoxybenzoates. Previously we have reported facile synthesis of 1,1′-binaphthyl-2-carboxylates via the S_NAr reaction of alkyl 1-alkoxy-2-naphthoates by 1-naphthyl Grignard reagents.[10)] It is noted that isopropyl ester is bulky enough to prevent the Grignard addition to the ester carbonyl group. However, this methodology cannot simply be applied to the construction of the biphenyl system. Thus, treatment of isopropyl 2-methoxybenzoate **1e** with phenylmagnesium bromide **2a** (2 equiv) in diethyl ether–benzene at ambient temperature for 3 h resulted in the formation of diphenyl(2-methoxyphenyl)methanol **4** in good yield with no detectable amount of the S_NAr product (Scheme 2). Actually the reaction of a benzoate with Grignard reagents is one of the most established routes to triarylmethanols.[11)]

It was found, however, that the reaction of 2-methoxybenzoates **1** with **2a** could be controlled by the bulk of the ester moiety of **1** to give whether the carbonyl addition product **4** or the S_NAr product **3** (Runs 1—3 in Table 1). Thus, the reaction of 2,4,6-trimethylphenyl 2-methoxybenzoate **1a** with **2a** gave the biphen-



Scheme 1.



Scheme 2.

Table 1. Synthesis of Biphenyl-2-carboxylic Acids **6**

Run	Biphenyl coupling										Hydrolysis			
	1			**2**				Conditions[b]		**3** Yield[c]	Conditions[f]		**6** Yield[h]	
		R	R′ [a]		R^1	R^2	R^3	Solvent	Temp (Time/h)	%	Method	Time/h		%
1	**1a**	H	Mes	**2a**	H	H	H	A	r. t. (6)	**3a** 56	I	0.5	**6a**	91
2	**1b**	H	DIPP					A	r. t. (12)	**3b** 71	I	0.5		90
3	**1c**	H	BHT					A	r. t. (20)–refl. (1)	**3c** 96	II	1.5		100
4								B	r. t. (20)–refl. (3)	92				—[i]
5	**1b**	H	DIPP	**2b**	MeO	H	H	A	r. t. (1)	**3d** 0[d]			**6b**	
6	**1c**	H	BHT					A	r. t. (1)	**3e** 98	II	1.5		100
7								B	r. t. (20)	94				—[i]
8	**1a**	H	Mes	**2c**	Me	H	H	A	r. t. (20)	**3f** 70	I	0.5	**6c**	97
9	**1b**	H	DIPP					A	r. t. (20)	**3g** 85	I	1.0		97
10	**1c**	H	BHT					A	r. t. (20)–refl. (1)	**3h** 96	II	1.5		95
11								B	refl. (24)	90				—[i]
12	**1b**	H	DIPP	**2d**	MeO	MeO	H	B	r. t. (6)–refl. (12)	**3i** 0[d]			**6d**	
13	**1c**	H	BHT					B	refl. (48)	**3j** 74	II	9.0[g]		97
14	**1d**	Me	BHT					C	refl. (24)	**3k** 91			**6e**	—[i]
15	**1a**	H	Mes	**2e**	Me	Me	Me	A	refl. (12)	**3l** 68	I	1.0	**6f**	90
16	**1b**	H	DIPP					A	refl. (12)	**3m** 80	I	2.5		90
17	**1c**	H	BHT					A	refl. (36)	**3n** 0[e]				

a) Mes=2,4,6-trimethylphenyl; DIPP=2,6-diisopropylphenyl; BHT=2,6-di-*t*-butyl-4-methylphenyl. b) Conditions of biphenyl coupling: **1**, 2.00 mmol; **2**/**1**=2 (mol/mol). Solvent: A, Et_2O (7 ml)–PhH (14 ml); B, THF (15 ml); C, THF (10 ml)–PhH (10 ml). c) Based on isolated pure products. d) Attack to the ester carbonyl. e) 2,6-Di-*t*-butyl-4-methylphenyl salicylate (**5**, 56%) was isolated. f) Conditions of hydrolysis of **3** by method I: **3**, 50.0 mg; KOH, 230 mg; water (0.1 ml)–EtOH (2.0 ml); reflux. Method II: **3**, 50.0 mg; MeOH/**3**=20 (mol/mol); NaH/**3**=10 (mol/mol); PhMe (1.5 ml)–HMPA (0.3 ml); reflux. g) After 9 h, water (0.1 ml) was added and the mixture was refluxed for further 0.5 h. h) Based on crude products. i) Not examined.

yl-2-carboxylate **3a** in 56% yield but accompanied the formation of the tertiary alcohol **4** (25%) (Run 1). The reaction of 2,6-diisopropylphenyl ester **1b** improved the yield of **3b** to 71% at the expense of the formation of **4** (21%) (Run 2). Eventually, 2,6-di-*t*-butyl-4-methylphenoxyl residue of **1c** completely suppressed the carbonyl addition and afforded the biphenyl product **3c** in an excellent yield (Run 3).

Synthesis of Biphenyl-2-carboxylates. Table 1 summarizes the results of the reaction of 2-methoxybenzoates **1** with aryl Grignard reagents **2** to give the biphenyl-2-carboxylates **3**. The results in Table 1 makes Fig. 1 for a guide of proper substrate–reagent combination to carry out the biphenyl coupling in synthetically useful yield. It can be seen that the aryl Grignard reagents not bearing 2-methoxyl substituent (**2a**, **2c**, and **2e**) react successfully with 2,6-diisopropylphenyl ester **1b** to give the biphenylcarboxylates **3** in good yields. Although the reaction of **2a** with **1b** accompanied the formation of **4** in appreciable quantities (Run 2), it should be noted that the yield of the biphenyl-2-carboxylate **3b** (71%) should be acceptable considering the easiness of the hydrolytic removal of the 2,6-diisopropylphenoxyl moiety (vide infra). Coupling product **3n** was not obtained by the reaction of 2,4,6-trimethylphenylmagnesium bromide **2e** with 2,6-di-*t*-butyl-4-methylphenyl ester **1c**; only demethylation of **1c** to give the 2-hydroxybenzoic ester **5** proceeded by presumably Lewis acid catalysis of the magnesium species present in the reaction mixture (Run 17).

Interestingly, the aryl Grignard reagents bearing 2-methoxyl group (**2b** and **2d**) required the 2,6-di-*t*-butyl-4-methylphenyl moiety to suppress the carbonyl addition (Runs 6 and 13). It seems that the coordination of the methoxyl group to magnesium center expels the ligating solvent molecules to reduce the apparent bulk of these phenyl carbanion species.[12] Evidence of strong coordination of the 2-methoxyl-oxygen to magnesium has been suggested for the highly efficient asymmetric induction in the binaphthyl axis formation by the reaction of 2-methoxy-1-naphthylmagnesium bromide with 1-alkoxy-2-naphthoates.[10] The effect of the reaction medium is also consistent with the above reasoning; the coupling reaction proceeds rather faster in diethyl ether–benzene than in tetrahydrofuran (THF). Grignard reagent **2d** is essentially insoluble in diethyl ether and necessitates the use of THF solvent, but the yield of the coupling product was greatly improved by diluting with benzene (Run 14).

Protection of the Carboxyl Group of 2-Methoxybenzoic Acid and Deprotection of the Biphenyl-2-carboxylates. Esters **1a** and **1b** were prepared by traditional procedure by treating 2-methoxybenzoyl chloride with the corresponding phenols, respectively, in the presence of 4-dimethylaminopyridine (DMAP). Sterically more congested 2,6-di-*t*-bu-

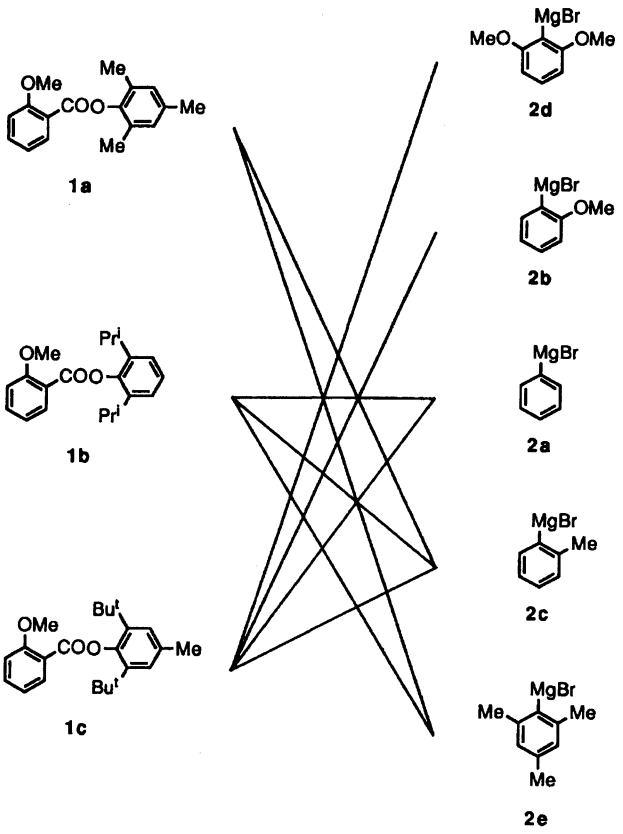
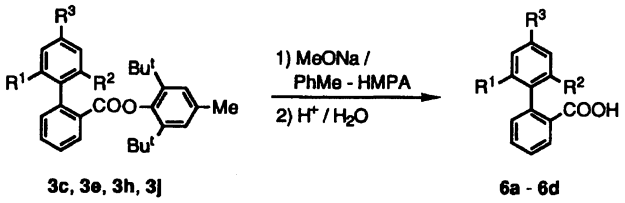


Fig. 1. The substrate–reagent combination for biphenyl synthesis.

tyl-4-methylphenyl esters (**1c** and **1d**) were also easily obtained by reacting 2-methoxybenzoic acids with the phenol in trifluoroacetic anhydride.[13]

After the S_NAr reaction of **1** with **2** to give the biphenyl-2-carboxylates **3**, removal of the 2,6-dialkylphenoxyl group was successfully carried out as follows. As mentioned above, hydrolytic deprotection of the 2,6-diisopropylphenoxyl moiety to give the free acids **6** is quite easy, needless to mention of the 2,6-dimethyl analog (Table 1). For example, hydrolysis of **3g** was completed in less than 1 h by heating at reflux in 10% potassium hydroxide solution in 95% ethanol (Run 9).

Carboxyl group has been conventionally protected from highly nucleophilic reagents by converting it into a 2,6-di-*t*-butylphenyl ester, but deprotection of the phenoxyl residue has been highly difficult in general and required troublesome manipulations.[14,15] To our best knowledge, hydrolysis of 2,6-di-*t*-butylphenyl esters have been unprecedented; 2,6-di-*t*-butyl-4-methoxyphenoxyl moiety has been frequently utilized as it can be oxidatively removed to liberate the free acid by treatment with cerium(IV) ammonium nitrate (CAN).[14] Herein, however, we have found that the treatment of 2,6-di-*t*-butyl-4-methylphenyl biphenyl-2-carboxylates with sodium methoxide in toluene–hexamethylphosphoric triamide (HMPA) (5/1 (vol/vol)) readily affords the free biphenyl-2-carboxylic acids (Scheme 3).

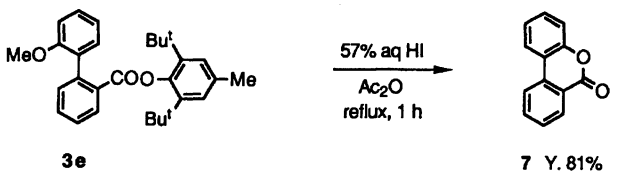


Scheme 3.

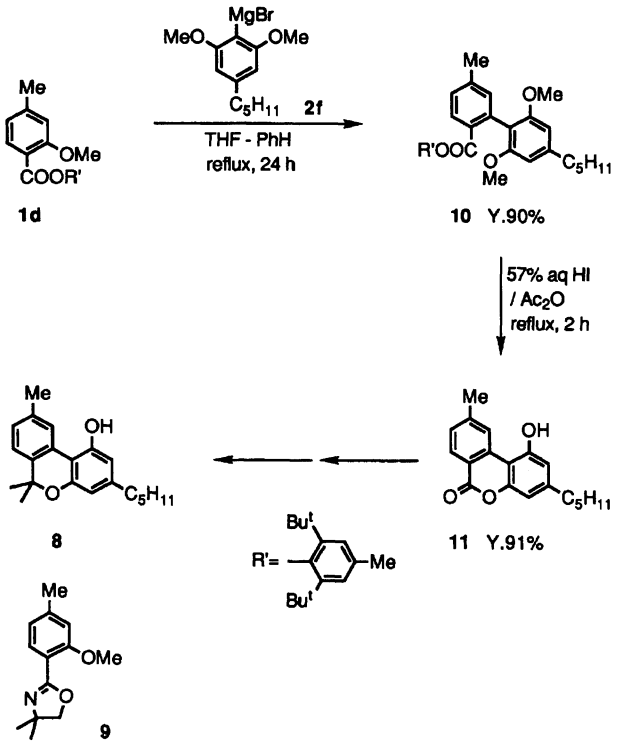
Although precise mechanism of the hydrolytic removal of the bulky 2,6-di-*t*-butylphenoxyl protecting group still remains to be elucidated, transesterification to the methyl ester may be the initial step, which is followed by hydrolysis to afford the free acids. It is obvious that the facile and simple deprotection procedure is of great synthetic value.

Chemists may not feel happy to use HMPA even as the cosolvent for the removal of the phenoxyl residue, but it does not devalue the present bipheny-coupling procedure. It should be recalled that only the phenyl Grignard regents bearing 2-methoxyl substituent necessarily require the use of the 2,6-di-*t*-butyl-4-methylphenoxyl protecting group on the 2-methoxybenzoate nucleus. The resulting 2′-methoxybiphenyl-2-carboxylates, however, can be deprotected by acidic treatment via demethylative lactonization to give the 6*H*-dibenzo[*b*,*d*]pyran-6-one (**7**) structure (e. g. Scheme 4), which is also prevailing in many natural products.[2]

Formal Synthesis of Cannabinol 8. Cannabinol (6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol) **8** is a constituent of *Cannabis sativa L* (marijuana), the synthesis of which has been the subject of interest.[16,17] The key-step of the synthesis of it is apparently the regioselective joining of two aryl halves for the construction of the biphenyl skeleton. Novák and Salemink utilized the Meyers reaction to effect this transformation by first converting 2-methoxy-4-methylbenzoic acid to a oxazoline **9** and then reacting it with 2,6-dimethoxy-4-pentylphenyl Grignard reagent.[16,18] Here we simplified the synthesis by use of the ester-activated S_NAr process (Scheme 5). 2-Methoxy-4-methylbenzoate **1d** was treated with 2 equiv of **2f** in THF–benzene at reflux for 24 h. After the usual workup, column chromatography on silica gel gave the biphenyl ester **10** in 90% yield. Demethylative lactonization of **10** by treatment with 57% aqueous hydrogen iodide in acetic anhydride at reflux for 2 h gave the lactone **11** in excellent yield (91%). Conversion of **11** into cannabinol **8** by treatment with



Scheme 4.



Scheme 5.

methyl Grignard reagent followed by acidification has been described in the literature.[19]

In conclusion, we have shown here a very convenient, regioselective aryl-coupling method for the synthesis of 1,1′-biphenyl-2-carboxylates by the reaction of readily available 2-methoxybenzoates with aryl Grignard reagents. It has also been shown for the first time that 2,6-di-*t*-butylphenyl benzoates can be easily hydrolyzed by treatment with sodium methoxide in toluene in the presence of HMPA.

Experimental

Measurements. IR spectra were measured on a Shimadzu IR-430 grating spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX60 instrument or a Bruker AC-250T instrument using tetramethylsilane as internal standard. Mass spectra were recorded on a JEOL JMS-D300 double focusing mass spectrometer with direct sample injection. Microanalyses were carried out in the Microanalytical Laboratory of the Institute for Chemical Reaction Science, Tohoku University. Melting points were measured on a Yamato MP-21 apparatus and are uncorrected unless otherwise noted.

Materials. Merck silica gel 60GF_{254} was used for analytical and preparative TLC. Silica-gel columns were prepared by use of Nacalai silica gel 60 (70—230 mesh). Water- and air-sensitive reactions were routinely carried out under a nitrogen atmosphere. Diethyl ether, benzene, and THF were distilled from sodium diphenylketyl just before use. Other solvents for experiments requiring anhydrous conditions were purified by usual methods. Commercial materials were used as purchased. 2-Bromo-1,3-dimethoxybenzene and 2-bromo-1,3-dimethoxy-5-pentylbenzene were synthesized according to the literature procedures.[20,16]

Preparation of 2-Methoxybenzoates 1. 2,4,6-Trimethylphenyl 2-Methoxybenzoate (1a): 2-Methoxybenzoic acid (6.15 g, 40.4 mmol) was heated under reflux for 3 h in thionyl chloride (20 ml) and volatiles were removed under reduced pressure. The acid chloride was dissolved in dry benzene (20 ml) and added dropwise to a mixture of 2,4,6-trimethylphenol (5.00 g, 36.7 mmol), 4-dimethylaminopyridine (DMAP) (4.49 g), benzene (20 ml), and pyridine (15 ml). Then the mixture was stirred at ambient temperature. After 4 h, 0.1 ml of *N*,*N*-dimethyl-1,3-propanediamine was added and the resulting mixture was diluted with benzene (20 ml). It was washed successively with 2 M# HCl, 2 M Na_2CO_3, and brine, and dried over $MgSO_4$. After volatiles were evaporated, the residue was chromatographed on a silica-gel column eluting with hexane–ethyl acetate (6/1) to give 8.42 g of **1a** as a colorless oil (85%); IR (liq. film) 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.19 (6H, s, $CH_3\times2$), 2.28 (3H, s, CH_3), 3.93 (3H, s, OCH_3), and 6.57—8.08 (6H, m, Ar-H). Found: C, 75.60; H, 6.65%. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

2,6-Diisopropylphenyl 2-Methoxybenzoate (1b): Ester **1b** was prepared by a similar procedure to that used for **1a**. 2-Methoxybenzoyl chloride prepared from 6.17 g of 2-methoxybenzoic acid (40.6 mmol) was treated with 2,6-diisopropylphenol (6.57 g, 36.9 mmol) in benzene–pyridine in the presence of 4.50 g of DMAP at ambient temperature overnight. Recrystallization from methanol gave 9.32 g of **1b** as colorless crystals (81%); mp 63.1—63.6 °C; IR (KBr) 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.22 (12H, d, J=6.6 Hz, $CH(\underline{CH_3})_2\times2$), 3.09 (2H, sept, J=6.6 Hz, CH×2), 3.92 (3H, s, OCH_3), and 6.91—8.07 (7H, m, Ar-H). Found: C, 76.91; H, 7.83%. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74%.

2,6-Di-*t*-butyl-4-methylphenyl 2-Methoxybenzoate (1c): The method was essentially that reported by Parish and Stock.[13] To a solution of 2-methoxybenzoic acid (2.78 g, 18.3 mmol) in trifluoroacetic anhydride (15 ml) was added 2,6-di-*t*-butyl-4-methylphenol (4.03 g, 18.3 mmol) and the mixture was stirred at ambient temperature for 4 h. After the mixture was diluted with benzene (100 ml), 50 ml of 2 M NaOH was carefully added. Then two layers were separated and the organic layer was washed successively with 2 M NaOH and water, and dried over $MgSO_4$. After the solvent was evaporated, the residue was recrystallized from ethanol to give 4.70 g of **1c** as colorless crystals (73%); mp 99.0—99.5 °C; IR (KBr) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.33 (18H, s, $C(CH_3)_3\times2$), 2.34 (3H, s, CH_3), 3.90 (3H, s, OCH_3), and 6.91—8.23 (6H, m, Ar-H). Found: C, 77.81; H, 8.58%. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53%.

2,6-Di-*t*-butyl-4-methylphenyl 2-Methoxy-4-methylbenzoate (1d): Ester **1d** was prepared by a similar procedure to that used for **1c**. 2-Methoxy-4-methylbenzoic acid[21] (3.04 g, 18.3 mmol) and 2,6-di-*t*-butyl-4-methylphenol (4.03 g, 18.3 mmol) were treated with 15 ml of trifluoroacetic anhydride. Recrystallization from diethyl ether gave 6.12 g of **1d** as colorless crystals (91%); mp 150 °C; IR (KBr) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.32 (18H, s, $C(CH_3)_3\times2$), 2.33 (3H, s, CH_3), 2.42 (3H, s, CH_3), 3.89 (3H, s, OCH_3), and 6.83—8.11 (5H, m, Ar-H). Found: C, 78.13; H, 8.85%.

#1 M=1 mol dm^{-3}.

Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75%.

Isopropyl 2-Methoxybenzoate (1e): Ester **1e** was prepared by a similar procedure to that used for **1a**. 2-Methoxybenzoyl chloride prepared from 6.00 g of 2-methoxybenzoic acid (39.4 mmol) was treated with 2-propanol (2.82 g, 46.9 mmol) in benzene–pyridine in the presence of 4.86 g of DMAP under reflux for 3 h. Distillation under reduced pressure (bp 74.0—76.0 °C/0.5 mmHg## (lit,[22] 129—133 °C/13 mmHg)) to give 4.81 g of **1e** as a colorless oil (63%); IR (liq. film) 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.36 (6H, d, J=6.6 Hz, $CH(\underline{CH_3})_2$), 3.89 (3H, s, OCH_3), 5.25 (1H, sept, J=6.6 Hz, CH), and 6.81—7.83 (4H, m, Ar-H).

Synthesis of Biphenyl-2-carboxylates 3. General procedure for Grignard reaction was similar to that described in the previous paper.[10] To a solution of **1** (2.00 mmol) in dry benzene (7 ml) was added **2** which was prepared from the corresponding aryl bromide (4.00 mmol) and magnesium turnings (0.16 g) in dry diethyl ether (7 ml) and dissolved by addition of 7 ml of benzene. The mixture was stirred for 1—48 h at appropriate temperature. In case of the reaction using THF (solvent B in Table 1) or THF–benzene (solvent C) as the solvent, **2** was prepared from aryl bromide (4.00 mmol) and magnesium turnings (0.16 g) in THF (10 ml) and added to a solution of **1** (2.00 mmol) in THF (5 ml) or benzene (10 ml) respectively. See Table 1 for reaction conditions and the yield of **3**. Chromatography on a silica-gel column was used for purification of the products using indicated eluent unless otherwise noted.

3a: After volatiles which contained 2,4,6-trimethylphenol derived from Grignard addition to the ester carbonyl group were distilled out by use of Kugelrohr (50 °C/0.3 mmHg), the residue was chromatographed on a silica-gel column eluting with hexane–benzene (1/1) to give pure **3a**; mp 169—170 °C; IR (KBr) 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.04 (6H, s, CH_3×2), 2.23 (3H, s, CH_3), and 6.82—8.15 (11H, m, Ar-H); MS (70 eV) m/z (rel intensity) 316 (M^+; 3), 182 (15), 181 (M-OR′; 100), 153 (16), 152 (20), and 136 (11).

3b: After volatiles which contained 2,6-diisopropylphenol derived from Grignard addition to the ester carbonyl group were distilled out by use of Kugelrohr (50 °C/2 mmHg), the residue was chromatographed on a silica-gel column eluting with hexane–benzene (1/1) to give pure **3b**; IR (liq. film) 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.13 (12H, d, J=7.1 Hz, $CH(\underline{CH_3})_2$×2), 2.87 (2H, sept, J=7.1 Hz, CH×2), and 7.12—8.23 (12H, m, Ar-H); MS (70 eV) m/z (rel intensity) 358 (M^+; 2), 182 (14), 181 (M-OR′; 100), 153 (14), and 152 (16).

3c: Hexane–ethyl acetate (19/1) as the eluent; mp 210—211 °C; IR (KBr) 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.29 (18H, s, $C(CH_3)_3$×2), 2.26 (3H, s, CH_3), and 7.05—8.52 (11H, m, Ar-H); MS (70 eV) m/z (rel intensity) 400 (M^+; 0.2), 182 (14), 181 (M-OR′; 100), 153 (11), and 152 (11).

3e: Benzene as the eluent; mp 192—194 °C; IR (KBr) 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.23 (9H, s, $C(CH_3)_3$), 1.33 (9H, s, $C(CH_3)_3$), 2.25 (3H, s, CH_3), 3.60 (3H, s, OCH_3), and 6.71—8.56 (10H, m, Ar-H); MS (70 eV) m/z (rel intensity) 430 (M^+; 0.2), 213 (16), 211 (M-OR′; 100), and 196 (12).

3f: Hexane–benzene (1/2) as the eluent; mp 108—109 °C; IR (KBr) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.93 (6H, s, CH_3×2), 2.12 (3H, s, CH_3), 2.20 (3H, s, CH_3), and 6.78—8.26 (10H, m, Ar-H); MS (70 eV) m/z (rel intensity) 330 (M^+; 3), 196 (16), 195 (M-OR′; 100), 167 (11), 166 (15), 152 (11), and 136 (16).

3g: After volatiles were removed by the same procedure as mentioned for **3b**, the residue was chromatographed on a silica-gel column eluting with hexane–ethyl acetate (10/1) to give pure **3g**; mp 84.5—85.7 °C; IR (KBr) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.08 (12H, d, J=7.1 Hz, $CH(\underline{CH_3})_2$×2), 2.12 (3H, s, CH_3), 2.73 (2H, sept, J=7.1 Hz, CH×2), and 7.09—8.25 (11H, m, Ar-H); MS (70 eV) m/z (rel intensity) 372 (M^+; 3), 196 (17), 195 (M-OR′; 100), and 165 (12).

3h: Hexane–benzene (1/1) as the eluent; mp 219—220 °C; IR (KBr) 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.23 (9H, s, $C(CH_3)_3$), 1.32 (9H, s, $C(CH_3)_3$), 1.99 (3H, s, CH_3), 2.25 (3H, s, CH_3), and 6.88—8.55 (10H, m, Ar-H); MS (70 eV) m/z (rel intensity) 414 (M^+; 0.2), 196 (16), and 195 (M-OR′; 100).

3j: After volatiles which contained 1,3-dimethoxybenzene derived from the Grignard reagent were distilled out by use of Kugelrohr (50 °C/4 mmHg), the residue was chromatographed on a silica-gel column eluting with benzene to give pure **3j**; mp 252—253 °C; IR (KBr) 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28 (18H, s, $C(CH_3)_3$×2), 2.26 (3H, s, CH_3), 3.57 (6H, s, OCH_3×2), and 6.43—8.59 (9H, m, Ar-H); MS (70 eV) m/z (rel intensity) 460 (M^+; 0.2), 242 (16), 241 (M-OR′; 100), 226 (13), and 57 (13).

3k: After volatiles were removed by the same procedure as mentioned for **3j**, the residue was chromatographed on a silica-gel column eluting with benzene to give pure **3k**; mp 225—226 °C; IR (KBr) 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.27 (18H, s, $C(CH_3)_3$×2), 2.25 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.58 (6H, s, OCH_3×2), and 6.43—8.46 (8H, m, Ar-H); MS (70 eV) m/z (rel intensity) 256 (18), 255 (M-OR′; 100), and 240 (11). Found: C, 78.39; H, 8.15%. Calcd for $C_{31}H_{38}O_4$: C, 78.45; H, 8.07%.

3l: After volatiles were removed by the same procedure as mentioned for **3a**, the residue was chromatographed on a silica-gel column eluting with hexane–benzene (1/1) to give pure **3l**; mp 123 °C; IR (KBr) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.91 (6H, s, CH_3×2), 1.96 (6H, s, CH_3×2), 2.20 (3H, s, CH_3), 2.26 (3H, s, CH_3), and 6.78—8.26 (8H, m, Ar-H); MS (70 eV) m/z (rel intensity) 358 (M^+; 8), 224 (18), 223 (M-OR′; 100), 195 (13), 181 (11), and 166 (10).

3m: After volatiles were removed by the same procedure as mentioned for **3b**, the residue was chromatographed on a silica-gel column eluting with hexane–benzene (1/1) to give pure **3m**; mp 69.6—71.5 °C; IR (KBr) 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.07 (12H, d, J=6.8 Hz, $CH(\underline{CH_3})_2$×2), 1.97 (6H, s, CH_3×2), 2.27 (3H, s, CH_3), 2.66 (2H, sept, J=6.8 Hz, CH×2), and 6.87—8.24 (9H, m, Ar-H); MS (70 eV) m/z (rel intensity) 400 (M^+; 7), 224 (18), 223 (M-OR′; 100), and 195 (11).

Reaction of Isopropyl 2-Methoxybenzoate (1e) with Phenylmagnesium Bromide (2a). Ester **1e** (0.384 g, 1.98 mmol) was treated with 2 equiv of **2a** in diethyl ether (7 ml)–benzene (14 ml) by a similar procedure to that used for **3**. After the usual workup, solvents were evaporated and the residue was chromatographed on a silica-gel column eluting with hexane–benzene (1/1) to give 0.428 g

##1 mmHg=133.322 Pa.

of **4** as colorless crystals (75%); mp (corrected) 130—131 °C (lit,[23] 132 °C); IR (KBr) 3475 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.65 (3H, s, OCH_3), 5.30 (1H, s, OH), and 6.49—7.32 (14H, m, Ar-H).

Preparation of Biphenyl-2-carboxylic Acids 6. Compounds **6** were obtained by treatment of their 2,4,6-trimethylphenyl or 2,6-diisopropylphenyl esters with KOH in aqueous methanol (method I) or 2,6-di-*t*-butyl-4-methylphenyl esters with sodium methoxide in toluene–HMPA (method II). Preparation of biphenyl-2-carboxylic acid (**6a**) form **3a**—**3c** is described as typical examples.

Method I (Hydrolysis of 3a): A mixture of 50.2 mg of **3a** (0.159 mmol), KOH (230 mg), water (0.1 ml), and ethanol (2.0 ml) was refluxed for 0.5 h under nitrogen. After most of the ethanol was evaporated, 10 ml of water was added and the resulting mixture was acidified by addition of concd HCl. Then it was extracted several times with diethyl ether. After the solvent was evaporated, the residue was dissolved in diethyl ether (10 ml)–1 M $NaHCO_3$ (10 ml) and two layers were separated. The organic layer was extracted several times with 1 M $NaHCO_3$ and the combined aqueous layer was acidified by addition of concd HCl to liberate the free acid. Then it was extracted several times with diethyl ether and the combined extracts were washed with water, and dried over $MgSO_4$. After the solvent was evaporated, the residue was dried in vacuo to give 28.7 mg of **6a** as colorless crystals (91%); mp (corrected) 111—113 °C (lit,[24] 114 °C); IR (KBr) 2925 and 1687 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.29—7.96 (9H, m, Ar-H).

Hydrolysis of **3b** by a similar procedure used for **3a** also gave **6a**.

Method II (Hydrolysis of 3c): To a suspension of NaH (60% dispersion in mineral oil, 50.0 mg, 1.25 mmol) in toluene (1.5 ml) was added 0.10 ml of methanol (2.5 mmol) under nitrogen and the mixture was stirred at ambient temperature for 10 min. Then 0.3 ml of HMPA and 49.5 mg of **3c** (0.124 mmol) were added and the resulting mixture was refluxed for 1.5 h. After being cooled to ambient temperature, the mixture was poured into 2 M HCl (10 ml) and extracted several times with diethyl ether. After the solvent was evaporated, the residue was worked up as mentioned for method I (vide supra) to give 24.5 mg of **6a** as colorless crystals (100%), which showed the same IR and ^1H NMR spectra as those obtained from method I.

Similar reactions gave the following biphenyl-2-carboxylic acids **6**; the crude products were not further purified unless otherwise noted and their melting point are corrected. See Table 1 for reaction conditions and the yield of **6**.

6b: Mp 150—152 °C (lit,[24] 152—153 °C); IR (KBr) 2940 and 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.68 (3H, s, OCH_3) and 6.84—7.93 (8H, m, Ar-H).

6c: Mp 104—105 °C (lit,[24] 104—105 °C); IR (KBr) 2960 and 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.06 (3H, s, CH_3) and 7.05—8.04 (8H, m, Ar-H).

6d: Compound **3j** was treated with sodium methoxide in toluene–HMPA under reflux for 9 h as above. At the end of the reaction, 0.1 ml of water was added and the resulting mixture was refluxed for further 0.5 h to give **6d**; mp 217—219 °C (lit,[25] 218—220 °C); IR (KBr) 2930 and 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.68 (6H, s, $OCH_3\times2$) and 6.60—8.01 (7H, m, Ar-H).

6f: Recrystallization from ethyl acetate gave pure **6f**; mp 181—182 °C; IR (KBr) 2975 and 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.90 (6H, s, $CH_3\times2$), 2.33 (3H, s, CH_3), and 6.90—8.10 (6H, m, Ar-H). Found: C, 79.82; H, 6.68%. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

Synthesis of 6*H*-Dibenzo[*b*,*d*]pyran-6-one (7). To a hot solution of **3e** (50.8 mg, 0.118 mmol) in acetic anhydride (3 ml) was added dropwise 57% aq HI (3 ml) and the mixture was refluxed for 1 h. To the cooled mixture was added 30 ml of water and it was extracted several times with diethyl ether. The combined extracts were washed successively with 20% Na_2SO_3, 1 M $NaHCO_3$, and water and dried over $MgSO_4$. After the solvent was evaporated, the residue was purified by preparative TLC with hexane–ethyl acetate (4/1) as the eluent to give 18.7 mg of **7** as colorless crystals (81%); mp (corrected) 89.5—91.6 °C (lit,[26] 91—93 °C); IR (KBr) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.96—8.46 (8H, m, Ar-H).

Formal Synthesis of Cannabinol 8. 2,6-Di-*t*-butyl-4-methylphenyl 2′,6′-Dimethoxy-5-methyl-4′-penthyl-1,1′-biphenyl-2-carboxylate (10): This compound was synthesized by a similar procedure to that used for the synthesis of **3**. To a solution of **1d** (0.590 g, 1.60 mmol) in dry benzene (8 ml) was added 2,6-dimethoxy-4-pentylphenylmagnesium bromide (**2f**) which was prepared from the corresponding aryl bromide (0.930 g, 3.24 mmol) and magnesium turnings (0.13 g) in dry THF (8 ml), and the mixture was refluxed for 24 h. To the cooled mixture was added 50 ml of 2 M HCl and two layers were separated. After the organic layer was diluted with diethyl ether, it was washed successively with 2 M HCl, 2 M Na_2CO_3, and water and dried over $MgSO_4$. After the solvent was evaporated, volatiles which contained 1,3-dimethoxy-5-pentylbenzene were distilled out by use of Kugelrohr (100 °C, 1 mmHg). The residue was chromatographed on a silica-gel column eluting with hexane–dichloromethane (3/1) to give 0.787 g of **10** as colorless crystals (90%); mp 164—165 °C; IR (KBr) 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (3H, t, J=6.6 Hz, $(CH_2)_4\underline{CH_3}$), 1.27 (18H, s, $C(CH_3)_3\times2$), 1.27—1.36 (4H, m, $(CH_2)_2(\underline{CH_2})_2Me$), 1.55—1.66 (2H, m, $CH_2\underline{CH_2}Pr^n$), 2.25 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.53 (2H, t, J=7.9 Hz, CH_2Bu^n), 3.57 (6H, s, $OCH_3\times2$), 6.33 (2H, s, Ar-H), 7.05 (2H, s, Ar-H), 7.09 (1H, s, Ar-H), 7.32 (1H, d, J=8.1 Hz, Ar-H), and 8.39 (1H, d, J=8.1 Hz, Ar-H).

1-Hydroxy-9-methyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (11): This compound was synthesized by a similar procedure to that used for the synthesis of **7**. To a hot solution of **10** (500 mg, 0.918 mmol) in acetic anhydride (5 ml) was added dropwise 57% aq HI (5 ml) and the mixture was refluxed for 2 h. To the cooled mixture was added 30 ml of water and it was worked up as above. After the solvent was evaporated and the residue was chromatographed on a silica-gel column eluting with hexane–ethyl acetate (4/1) to give 248 mg of **11** as colorless crystals (91%); mp 191—192 °C (lit,[16] 185 °C); IR (KBr) 3350 and 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.88 (3H, t, J=6.6 Hz, $(CH_2)_4\underline{CH_3}$), 1.28—1.37 (4H, m, $(CH_2)_2(\underline{CH_2})_2Me$), 1.57—1.69 (2H, m, $CH_2\underline{CH_2}Pr^n$), 2.54 (3H, s, CH_3), 2.59 (2H, t, J=7.7 Hz, $\underline{CH_2}Bu^n$), 6.53 (1H, s, OH), 6.65 (1H, d, J=1.4 Hz, Ar-H), 6.80 (1H, d, J=1.4 Hz, Ar-H), 7.34 (1H, d, J=8.1 Hz, Ar-H), 8.32 (1H, d, J=8.1 Hz, Ar-H), and 8.85 (1H, s, Ar-H). Found: C, 77.21; H, 6.84%. Calcd for $C_{19}H_{20}O_3$: C,

77.00; H, 6.80%.

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