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Synthesis of Malabaricones, Diarylnonanoids Occurring in Myristicaceous Plants

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Naturally occurring diarylnonanoids, malabaricones A, B, C, D, and 1-(2-hydroxy-6-methoxyphenyl)-9-(3,4-methylenedioxyphenyl)-nonan-1-one were synthesized from a common intermediate, 6-benzyloxyhexyltriphenyl phosphonium bromide, by use of the Wittig reaction and crossed aldol reaction as key steps.

Keywords malabaricone; diarylnonanoid; Myristicaceae; synthesis; 6-benzyloxyhexyltriphenyl phosphonium bromide; Wittig reaction; crossed aldol reaction; dehydration

The plants of Myristicaceae characteristically contain a group of compounds classified as diarylnonanoids (Table I), all of which are derivatives of 2,6-dihydroxyacetophenone and are considered to be biosynthesized from a phenylpropanoid and six C_2 units. Malabaricones A—D are the typical examples,[1a)] and one of them (malabaricone C) was recently suggested to have significant biological activities (such as nematocidal,[1c)] bacteriocidal,[2)] and antioxidant[3)] activities). So far, only one report on the synthesis of malabaricone A has appeared.[4)] This paper describes our synthesis of the above diarylnonanoids.

Our synthetic scheme is indicated in Chart 1. We chose a hexane unit differently substituted at the two termini, *e.g.* 6-benzyloxyhexylphosphonium salt, as a common intermediate. The C–C bond formations at ① and ② followed by additional manipulations were expected to lead to the desired diarylnonanoids.

Results and Discussion

Syntheses of the Common Intermediate 5 and 7-Arylheptanols 7 Based on the results of preliminary experiments, we chose a benzyl group for protection of one terminus of hexanediol. Acetals such as an ethoxyethyl or an acetyl group were not appropriate because of their susceptibility to bromination or low selectivity in monoprotection.

1,6-Hexanediol mono-benzyl ether **2**[5)] was obtained in 46% yield on mono-benzylation of 1,6-hexanediol and converted to the bromide **3** in 88% yield by *N*-bromosuccinimide and triphenylphosphine according to a known procedure[6)] with some modifications. Heating of **3** with triphenylphosphine at 140 °C without solvent gave the expected phosphonium salt **4** in 75% yield.

The phosphonium salt **4** was converted to the ylide with potassium *tert*-butoxide (*tert*-BuOK) in tetrahydrofuran

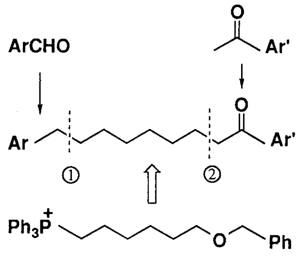
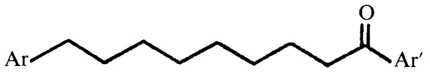
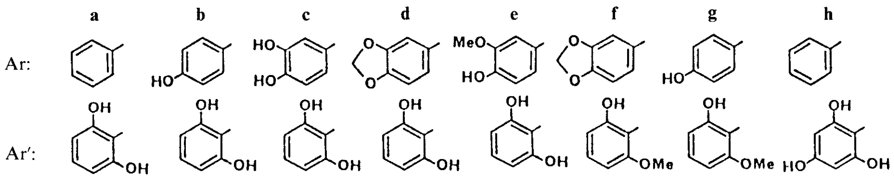


Chart 1

TABLE I. Naturally Occurring Diarylnonanoids



Compd.	Name	Botanical sources	References
1a	Malabaricone A	*Myristica malabarica* LAM.	1*a*)
		M. dactyloides GAERTN.	1*b*, *c*)
1b	Malabaricone B	*M. malabarica* LAM.	1*a*)
		M. dactyloides GAERTN.	1*b*, *c*)
1c	Malabaricone C	*M. malabarica* LAM.	1*a*)
		M. dactyloides GAERTN.	1*b*)
		M. fragrans HOUTT.	1*d*)
1d	Malabaricone D	*M. malabarica* LAM.	1*a*)
		M. dactyloides GAERTN.	1*b*, *c*)
1e	No name	*M. dactyloides* GAERTN.	1*b*)
1f	No name	*M. dactyloides* GAERTN.	1*c*)
1g	No name	*M. dactyloides* GAERTN.	1*c*)
1h	No name	*M. glabla* BL. (*Horsfieldia glabla* WARB.)	1*c*)



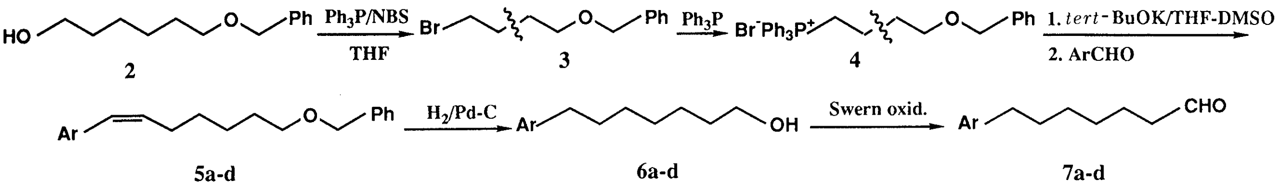


Chart 2

for **a**—**d**, see Table II

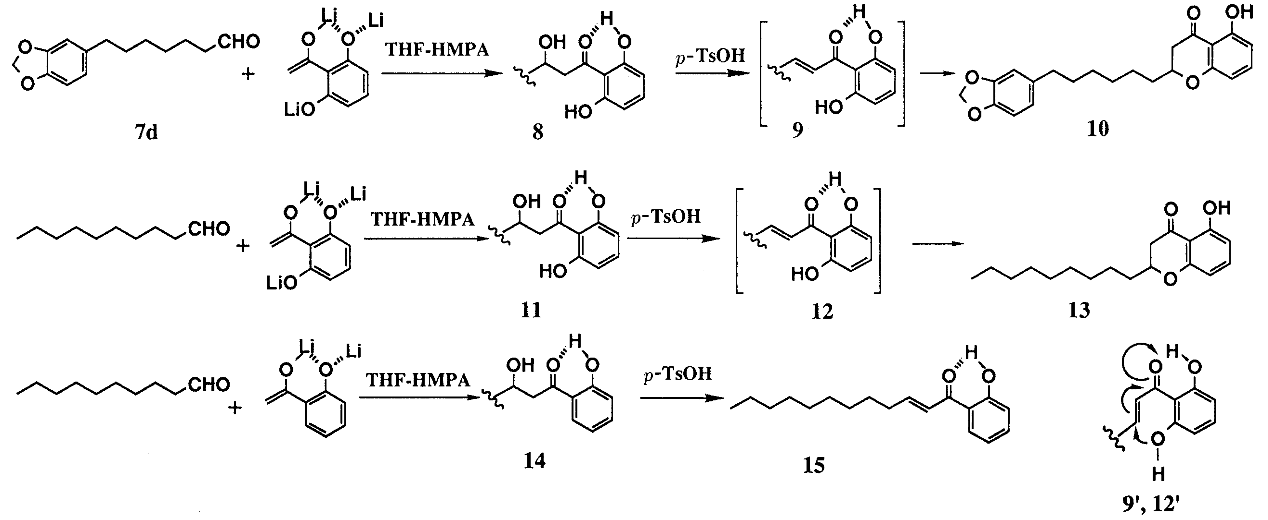
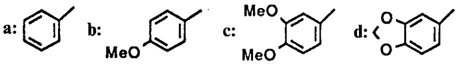


Chart 3

Table II. Yields in the Conversions of **4**→**5**→**6**→**7** (see Chart 2)

Ar	Yield (%)		
	4⟶5	⟶6	⟶7
a	49	93	98
b	69	85	95
c	71	83	98
d	75	92	98

Ar: for **5**—**7**



(THF)–dimethyl sulfoxide (DMSO) and allowed to react with various aromatic aldehydes to yield 7-arylheptenol benzyl ethers **5** in 50—75% yield (Table II). Sonication during the formation of the ylide increased the yields of **5**. The configurations of the olefinic moiety in **5** are mainly *Z* as evidenced from the coupling constant of $J = 11.5\,\text{Hz}$[7]) for the two olefinic protons in the proton nuclear magnetic resonance (^{1}H-NMR) spectra.

Hydrogenation of **5** in ethanol over 10% Pd–C gave, with concomitant hydrogenolysis of the benzyl group, the 7-arylheptanols **6** in high yields.

Synthesis of Malabaricones The 7-arylheptanol **6d** was subjected to Swern oxidation and the resulting aldehyde **7d** was coupled with the tri-anion derived from 2,6-dihydroxyacetophenone and 3 mol eq of lithium diisopropylamide (LDA) in THF–hexamethylphosphoric triamide (HMPA) to give the aldol product **8** in 38% yield. Without HMPA no aldol product was obtained.

Treatment of **8** with a catalytic amount of *p*-toluenesulfonic acid (TsOH) gave the chromanone derivative **10** (66% yield), instead of the expected conjugated ketone **9**. Model experiments of this dehydration reaction on the 2-hydroxy and 2,6-dihydroxy derivatives, **14** and **11**, revealed that the mono-phenolic compound **14** gave the expected conjugated ketone **15** smoothly, while the diphenolic compound **11** gave the chromanone **13** exclusively on the same treatment. This indicated that one of the *ortho*-phenolic group is strongly hydrogen bonded to the carbonyl group, and therefore, although the conjugated ketones are formed by dehydration, the free phenolic hydroxy group in the 2,6-dihydroxy compounds (*e.g.* **9′** and **12′**) rapidly adds in a Michael fashion to the conjugated enone, while the hydroxy group in 2-hydroxy compounds is masked by hydrogen bonding and does not add to the conjugated enone.

Therefore the 7-arylheptanals **7** prepared by Swern oxidation of **6** were subjected to aldol condensation with the di-anion derived from 2-benzyloxy-6-hydroxyacetophenone as described above. Addition of HMPA was again necessary to obtain the products in these reactions. The resulting aldol products **16** were smoothly dehydrated to the conjugated ketones **17** as expected.

Hydrogenation of **17** in acetone (for preventing over-reduction of the carbonyl group) over 10% Pd–C gave, with concomitant hydrogenolysis of the benzyl group, the saturated 2,6-dihydroxyacetophenone derivatives **18**. Compounds **18a**, mp 78—80 °C, and **18d**, mp 91—92 °C, were identical with malabaricone A (**1a**) and malabaricone D (**1d**), respectively.

Compounds **18b** and **18c** were demethylated with boron tribromide in dichloromethane to give the phenols of mp 102—104 °C and mp 119—121 °C, which were identical with malabaricones B (**1b**) and C (**1c**), respectively.

In a similar manner, 1-(2-hydroxy-6-methoxyphenyl)-9-(3,4-methylenedioxyphenyl)nonan-1-one **18e**, mp 52—53 °C, was synthesized starting from **7d** and 2-hydroxy-6-

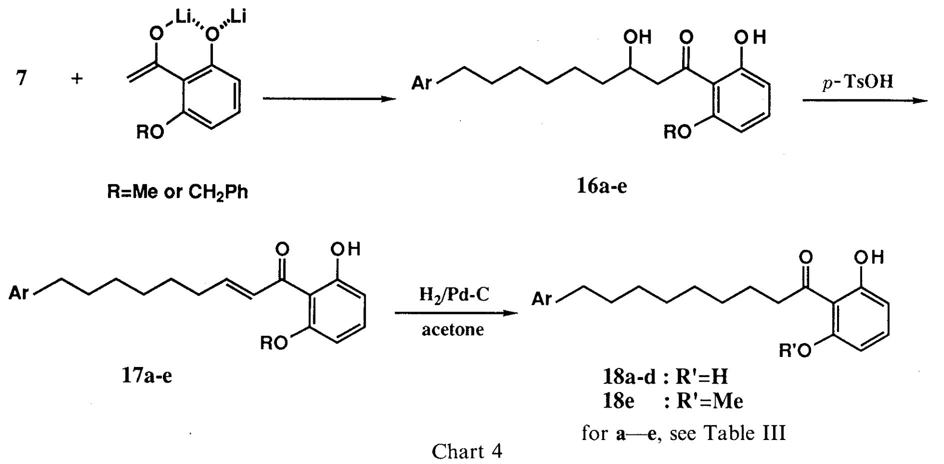
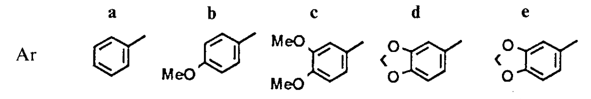


Chart 4

Table III. Yields in the Conversion of $7 \rightarrow 16 \rightarrow 17 \rightarrow 18$ (see Chart 4)

Ar	Yield (%)		
	$7 \longrightarrow 16$	$\longrightarrow 17$	$\longrightarrow 18$
a	71	86	89 (R' = H)
b	74	88	88 (R' = H)
c	73	91	88 (R' = H)
d	77	85	71 (R' = H)
e	100	90	91 (R' = Me)



	a	b	c	d	e
R or R'	$PhCH_2$	$PhCH_2$	$PhCH_2$	$PhCH_2$	Me

methoxyacetophenone and was shown to be identical with a natural diarylnonanoid **1e** found in *Myristica dactyloides.*[1d)]

The identities of the above synthesized diarylnonanoids with the natural compounds were confirmed by comparisons of their physical and spectral data with those reported.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage melting point apparatus and are uncorrected. Infrared (IR) spectra were taken for the $CHCl_3$ solutions on a JASCO A-202 spectrometer and are given in cm^{-1}. ^1H-NMR spectra were taken for the $CDCl_3$ solutions on a JEOL JNM-FX100 (FT-NMR; 100 MHz) spectrometer and are given in δ (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Aromatic protons indicated by ranges appeared as multiplets. Mass spectra (MS) were measured with a Hitachi H-80 mass spectrometer at an ionization voltage of 20 eV and major peaks are indicated by *m/z* (%). Ultraviolet (UV) spectra were measured in ethanol with a Hitachi 323 spectrometer and λ_{max} are given in nm (ε). Organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Column chromatography was performed on silica gel (Fuji-Davison BW-820MH).

6-Benzyloxyhexyl Bromide (3) *N*-Bromosuccinimide (9.9 g, 56 mmol) and PPh_3 (14.59 g, 56 mmol) were added to a stirred solution of 1,6-hexanediol mono-benzyl ether **2**[5)] (5.78 g, 28 mmol) in THF (200 ml) in several portions at room temperature. After 2 h, the reaction mixture was concentrated to half the initial volume and diluted with hexane. The precipitate was removed by filtration and the filtrate was concentrated to leave a residue, which was chromatographed to give **3** (6.63 g, 88%) as a colorless oil. ^1H-NMR: 1.20—2.00 (8H), 3.35 (2H, dd, $J=15$, 7 Hz, $-CH_2Br$), 3.50 (2H, dd, $J=15$, 6 Hz, $-CH_2O-$), 4.49 (2H, s, $PhCH_2O-$), 7.32 (5H, br s, Ph-H). MS: 272 and 270 (1 : 1, each 1%) (M^+ for ^{81}Br and ^{79}Br), 92 (100).

6-Benzyloxyhexyltriphenylphosphonium Bromide (4) Compound **3** (947 mg, 3.5 mmol) and PPh_3 (917 mg, 3.5 mmol) were heated at 140 °C for 2 h. The mixture was crystallized from acetone–ether to give **4** (1.39 g, 75%) as colorless prisms, mp 125—127.5 °C. ^1H-NMR: 1.24—1.80 (8H), 3.42 (2H, t, $J=6.5$ Hz, $-OCH_2-$), 3.74 (2H, m, $-P^+CH_2-$), 4.44 (2H, s, $-OCH_2Ph$), 7.49 (5H, s, Ph-H), 7.60—7.96 (15H, Ph-H). MS: 453 ($Ph_3PP^+(CH_2)_6OCH_2Ph$, 1), 262 (100). *Anal.* Calcd for $C_{31}H_{34}BrOP$: C, 69.54; H, 6.46. Found: C, 69.79; H, 6.42.

(*Z*)-1-Benzyloxy-7-arylhept-6-enes (5) (General Procedure) An aromatic aldehyde (10.5 mmol) in THF (5 ml) was added dropwise to a stirred solution of the ylide [9.5 mmol, prepared from *tert*-BuOK and **4** in THF–DMSO (25 : 1, 165 ml)] under an Ar atmosphere and the mixture was stirred for an additional 50 min with occasional sonication at room temperature. The reaction mixture was poured into ice-water, acidified with HCl and extracted with $CHCl_3$. Chromatography of the residue from the $CHCl_3$ extract gave the corresponding arylheptenol benzyl ether **5** in the yield indicated in Table II. The products were used directly for hydrogenation. The spectral data are as follows.

(*Z*)-1-Benzyloxy-7-phenylhept-6-ene (**5a**): This was prepared from **4** and benzaldehyde as a yellow oil. ^1H-NMR: 1.20—1.80 (6H), 2.19 (2H, m, $=CH\underline{H}_2-$), 3.45 (2H, t, $J=6.3$ Hz, $-CH_2O-$), 4.49 (2H, s, $-OCH_2Ph$), 5.59 (1H, dt, $J=11.5$, 7 Hz, $PhCH=C\underline{H}-$), 6.38 (1H, d, $J=11.5$ Hz, $PhC\underline{H}=CH-$), 7.08—7.38 (10H, Ph-H). MS: 280 (M^+, 2), 91 (100).

(*Z*)-1-Benzyloxy-7-(4-methoxyphenyl)hept-6-ene (**5b**): This was prepared from **4** and 4-methoxybenzaldehyde as a yellow oil. ^1H-NMR: 1.20—1.80 (6H), 2.28 (2H, m, $=CHC\underline{H}_2-$), 3.45 (2H, t, $J=6.3$ Hz, $-CH_2O-$), 3.78 (3H, s, OCH_3), 4.47 (2H, s, $PhCH_2O-$), 5.55 (1H, dt, $J=11.5$, 7.5 Hz, $ArCH=C\underline{H}-$), 6.34 (1H, br d, $J=11.5$ Hz, $ArC\underline{H}=CH-$), 6.82, 7.18 (each 2H, d, $J=8$ Hz, ArH), 7.30 (5H, br s, Ph-H). MS: 310 (M^+, 37), 121 (100).

(*Z*)-1-Benzyloxy-7-(3,4-dimethoxyphenyl)hept-6-ene (**5c**): This was prepared from **4** and 3,4-dimethoxybenzaldehyde as a yellow oil. ^1H-NMR: 1.29—1.76 (6H), 2.30 (2H, m, $=CHCH_2-$), 3.45 (2H, t, $J=6.3$ Hz, $-CH_2O-$), 3.86 (6H, s, $2 \times OCH_3$), 4.48 (2H, s, $PhCH_2O-$), 5.55 (1H, dt, $J=11.5$, 7.5 Hz, $ArCH=C\underline{H}-$), 6.33 (1H, br d, $J=11.5$ Hz, $ArC\underline{H}=CH-$), 7.25 (3H, br s, ArH), 7.31 (5H, br s, Ph-H). MS: 340 (M^+, 60), 151 (100).

(*Z*)-1-Benzyloxy-7-(3,4-methylenedioxyphenyl)hept-6-ene (**5d**): This was prepared from **4** and piperonal as a yellow oil. ^1H-NMR: 1.12—1.80 (6H), 1.92—2.45 (2H, m, $=CHC\underline{H}_2-$), 3.45 (2H, t, $J=6.3$ Hz, $-CH_2O-$), 4.48 (2H, s, $-OCH_2Ph$), 5.52 (1H, dt, $J=11.5$, 6.5 Hz, $ArCH=C\underline{H}-$), 5.93 (2H, s, $-OCH_2O-$), 6.28 (1H, dt, $J=11.5$, 2 Hz, $ArC\underline{H}=CH-$), 6.58—6.86 (3H, ArH), 7.30 (5H, br s, Ph-H). MS: 324 (M^+, 29), 135 (100).

7-Arylheptanols 6 (General Procedure) One of compounds **5** (6.5 mmol) in ethanol (50 ml) was hydrogenated over 10% Pd–C (0.8 g) at room temperature under hydrogen pressure of 4 kg/cm^2 for 24 h. Removal of the catalyst and the solvent from the mixtue left an oil which was purified by chromatography to give the corresponding arylheptanol **6** in the yield indicated in Table II.

7-Phenylheptanol (**6a**): Colorless oil. IR: 3620. ^1H-NMR: 1.18—1.76 (10H), 2.60 (2H, t, $J=7.8$ Hz, $PhCH_2-$), 3.62 (2H, t, $J=6.3$ Hz, $-C\underline{H}_2OH$), 7.04—7.36 (5H, Ph-H). MS: 192 (M^+, 26), 104 (100). High resolution mass spectra (HRMS) *m/z* (M^+): Calcd for $C_{13}H_{20}O$: 192.1513. Found: 192.1522.

7-(4-Methoxyphenyl)heptanol (**6b**): Colorless solid, mp < 30 °C. IR: 3620. ^1H-NMR: 1.12—1.76 (10H), 2.54 (2H, t, $J=7.8$ Hz, $ArCH_2-$), 3.60 (2H, br s, $-C\underline{H}_2OH$), 6.75, 7.08 (each 2H, d, $J=8.5$ Hz, ArH). MS: 222 (M^+, 91), 121 (100). HRMS *m/z* (M^+): Calcd for $C_{14}H_{22}O_2$: 222.1619.

Found: 222.1610.

7-(3,4-Dimethoxyphenyl)heptanol (**6c**): Colorless oil. IR: 3620. ^{1}H-NMR: 1.20—1.76 (10H), 2.56 (2H, t, $J=7.8$ Hz, ArCH$_2$–), 3.64 (2H, t, $J=6.3$ Hz, –C$\underline{\mathrm{H}}_2$OH), 3.86 (6H, s, 2×OCH$_3$), 6.60—6.84 (3H, ArH). MS: 252 (M$^+$, 46), 151 (100). HRMS m/z (M$^+$): Calcd for $C_{15}H_{24}O_3$: 252.1727. Found: 252.1719.

7-(3,4-Methylenedioxyphenyl)heptanol (**6d**): Colorless oil. IR: 3620. ^{1}H-NMR: 1.08—1.76 (10H), 2.52 (2H, t, $J=7.8$ Hz, ArCH$_2$–), 3.60 (2H, t, $J=6.3$ Hz, –C$\underline{\mathrm{H}}_2$OH), 5.93 (2H, s, –OCH$_2$O–), 6.48—6.80 (3H, ArH). MS: 236 (M$^+$, 55), 135 (100). HRMS m/z (M$^+$): Calcd for $C_{14}H_{20}O_3$: 236.1411. Found: 236.1405.

7-Arylheptanals 7 (General Procedure) A 7-arylheptanol (0.79 mmol) in CH$_2$Cl$_2$ (3 ml) was added to a stirred solution of DMSO (0.15 ml) and oxalyl chloride (0.16 ml) in CH$_2$Cl$_2$ (2 ml) at −78 °C. After 15 min, Et$_3$N (0.45 ml) was added and stirring was continued at −78 °C for 5 min, then at room temperature for 20 min. The reaction mixture was diluted with CH$_2$Cl$_2$, washed with 1 N HCl, and concentrated. Chromatography of the product gave the corresponding 7-arylheptanal **7** in the yield indicated in Table II. These compounds gave the following spectral data, and were used for the next step without further characterization.

7-Phenylheptanal (**7a**): Colorless oil. IR: 1720. ^{1}H-NMR: 1.05—1.81 (8H), 2.39 (2H, td, $J=7.5$, 2 Hz, –CH$_2$CHO), 2.59 (2H, t, $J=7.5$ Hz, PhCH$_2$–), 6.85—7.35 (5H, Ph-H), 9.70 (1H, t, $J=2$ Hz, –CHO). MS: 190 (M$^+$, 100).

7-(4-Methoxyphenyl)heptanal (**7b**): Colorless oil. IR: 1720. ^{1}H-NMR: 1.14—1.78 (8H), 2.40 (2H, td, $J=7.5$, 2 Hz, –C$\underline{\mathrm{H}}_2$CHO), 2.54 (2H, t, $J=7.5$ Hz, ArCH$_2$–), 3.78 (3H, s, OCH$_3$), 6.78, 7.06 (each 2H, d, $J=8$ Hz, ArH), 9.75 (1H, t, $J=2$ Hz, –CHO). MS: 220 (M$^+$, 27), 121 (100).

7-(3,4-Dimethoxyphenyl)heptanal (**7c**): Colorless oil. IR: 1717. ^{1}H-NMR: 1.18—1.86 (8H), 2.40 (2H, td, $J=7.5$, 2 Hz, –C$\underline{\mathrm{H}}_2$CHO), 2.54 (2H, t, $J=7.5$ Hz, ArCH$_2$–), 3.85, 3.87 (each 3H, s, 2×OCH$_3$), 6.50—6.82 (3H, ArH), 9.74 (1H, t, $J=2$ Hz, –CHO). MS: 250 (M$^+$, 36), 151 (100).

7-(3,4-Methylenedioxyphenyl)heptanal (**7d**): Colorless oil. IR: 1722. ^{1}H-NMR: 1.04—1.80 (8H), 2.43 (2H, td, $J=7.5$, 2 Hz, –C$\underline{\mathrm{H}}_2$CHO), 2.52 (2H, t, $J=7.5$ Hz, ArCH$_2$–), 5.90 (2H, s, –OCH$_2$O–), 6.55—6.76 (3H, ArH), 9.75 (1H, t, $J=2$ Hz, –CHO). MS: 234 (M$^+$, 80), 135 (100).

Benzylation of 2,6-Dihydroxyacetophenone 2,6-Dihydroxyacetophenone (0.5 g, 3.3 mmol) and NaH (131 mg, 3.3 mmol) in DMSO (10 ml) were stirred at room temperature for 10 min. Benzyl bromide (0.4 ml, 3.4 mmol) was added and stirring was continued for 1 h. The reaction mixture was poured into cold 1 N HCl and extracted with CH$_2$Cl$_2$. Chromatography of the product gave 2-benzyloxy-6-hydroxyacetophenone (610 mg, 76%), mp 109—110 °C, as yellow needles from benzene–ether. ^{1}H-NMR: 2.59 (3H, s, CH$_3$), 5.09 (2H, s, –OCH$_2$Ph), 6.44 (1H, d, $J=8$ Hz, ArH), 6.56 (1H, d, $J=8$ Hz, ArH), 7.30 (1H, t, $J=8$ Hz, ArH), 7.39 (5H, br s, Ph-H), 13.25 (1H, s, OH). MS: 242 (M$^+$). 2,6-Dibenzyloxyacetophenone (130 mg, 12%) was also obtained as a yellow gum. ^{1}H-NMR: 2.49 (3H, s, CH$_3$), 5.07 (4H, s, –OCH$_2$Ph×2), 6.59 (2H, d, $J=8$ Hz, ArH), 7.10—7.35 (11H, Ph-H and ArH). MS: 332 (M$^+$), 91 (100).

Condensation of 2,6-Dihydroxyacetophenone with Decanal and Dehydration of the Product [8-Hydroxy-2-nonylchroman-4-one (13)] 2,6-Dihydroxyacetophenone (0.5 g, 3.19 mmol) in THF (6 ml) was added dropwise to a solution of LDA (10 mmol) in THF (5 ml) over 5 min at −78 °C under an Ar atmosphere and the mixture was stirred for 15 min. A solution of *n*-decanal (0.66 ml, 3.5 mmol) and HMPA (1.8 ml, 10 mmol) in THF (6 ml) was added, and the reaction mixture was stirred at −78 °C for 50 min, and at 0 °C for 1 h, then poured into cold 10% HCl and extracted with AcOEt. Work-up of the extract gave an aldol (**11**, 263 mg). A solution of the aldol **11** and *p*-TsOH (134 mg, 0.7 mmol) in benzene (10 ml) was heated under reflux for 45 min. The cooled mixture was washed with saturated aqueous NaHCO$_3$, and concentrated. Chromatography of the residue gave the chromanone **13** (270 mg, 28% from 2,6-dihydroxyacetophenone) as a yellow oil. IR: 1641, 1626, 1573. ^{1}H-NMR: 0.88 (3H, br t, $J=7$ Hz, CH$_3$), 1.28 (16H, br s), 2.72 (2H, m, –CH$_2$CO–), 4.34 (1H, m, >CHO–), 6.36 (1H, dd, $J=8$, 1 Hz, ArH), 6.44 (1H, dd, $J=8$, 1 Hz, ArH), 7.32 (1H, t, $J=8$ Hz, ArH). MS: 290 (M$^+$, 12), 137 (100). HRMS m/z (M$^+$): Calcd for $C_{18}H_{26}O_3$: 290.1883. Found: 290.1889.

Condensation of *o*-Hydroxyacetophenone with Decanal and Dehydration of the Product [1-(2-Hydroxyphenyl)-2-dodecen-1-one (15)] *o*-Hydroxyacetophenone (1.13 g, 8.3 mmol) in THF (5 ml) was added dropwise to a solution of LDA (17.6 mmol) in THF (10 ml) over 5 min at −78 °C under an Ar atmosphere, and the mixture was stirred for 30 min. *n*-Decanal (1.7 ml, 9 mmol) in THF (8 ml) and HMPA (3.2 ml, 18.4 mmol) was added to this solution and the mixture was stirred for a further 1 h. Work-up of the reaction mixture as described above gave an aldol (**14**, 203 mg). The aldol **14** and *p*-TsOH (158 mg, 0.83 mmol) in benzene (20 ml) was heated under reflux for 4 h. Work-up of the mixture gave, after chromatography, the enone **15** (2 g, 88% from *o*-hydroxyacetophenone) as a yellow oil. IR: 1643, 1615, 1585. ^{1}H-NMR: 0.88 (3H, br t, $J=7$ Hz, CH$_3$), 1.00—1.50 (14H), 2.31 (2H, dt, $J=6$, 6.6 Hz, =CHCH$_2$–), 6.86 (1H, t, $J=8$ Hz, ArH), 6.96 (1H, d, $J=8$ Hz, ArH), 6.96 (1H, d, $J=15$ Hz, –COC$\underline{\mathrm{H}}$=CH–), 7.20 (1H, dt, $J=15$, 6 Hz, –COCH=C$\underline{\mathrm{H}}$–), 7.43 (1H, t, $J=8$ Hz, ArH), 7.76 (1H, d, $J=8$ Hz, ArH), 12.74 (1H, s, OH). MS: 274 (M$^+$, 6), 140 (100). HRMS m/z (M$^+$): Calcd for $C_{18}H_{26}O_2$: 274.1934. Found: 274.1934.

Condensation of 7-Arylheptanals (7) with 2-Benzyloxy-6-hydroxyacetophenone (General Procedure) 2-Benzyloxy-6-hydroxyacetophenone (0.58 mmol) in THF (4 ml) was added dropwise to a solution of LDA (2 mmol) in THF (3 ml) over 5 min at −78 °C under an Ar atmosphere and the mixture was stirred for 2 h. After addition of HMPA (0.5 ml), a 7-arylheptanal **7** (0.58 mmol) in THF (4 ml) was added dropwise to the above mixture over 5 min. The whole was stirred at −78 °C for 1 h, and at −15 °C for 30 min, then poured into cold 1 N HCl and extracted with CHCl$_3$. Work-up of the extract gave, on chromatography the corresponding aldol **16** in the yield indicated in Table III.

1-(2-Benzyloxy-6-hydroxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**16a**): Pale yellow prisms (from hexane–ether), mp 59—60 °C. IR: 1619, 1594. ^{1}H-NMR: 0.96—1.80 (10H), 2.60 (2H, t, $J=8$ Hz, PhCH$_2$–), 2.93 (1H, dd, $J=18$, 9 Hz) and 3.18 (1H, dd, $J=18$, 3 Hz) (–CH$_2$CO–), 4.02 (1H, m, >C$\underline{\mathrm{H}}$OH), 5.07 (2H, s, PhCH$_2$O–), 6.42 (1H, d, $J=8$ Hz, ArH), 6.56 (1H, d, $J=8$ Hz, ArH). 7.00—7.48 (11H, ArH and Ph-H). MS: 432 (M$^+$, 6), 91 (100). HRMS m/z (M$^+$): Calcd for $C_{28}H_{32}O_4$: 432.2302. Found: 432.2292.

1-(2-Benzyloxy-6-hydroxyphenyl)-3-hydroxy-9-(4-methoxyphenyl)nonan-1-one (**16b**): Pale yellow prisms (from hexane–ether), mp 40—41 °C. IR: 1618, 1593. ^{1}H-NMR: 0.92—1.60 (10H), 2.46 (2H, t, $J=8$ Hz, ArCH$_2$–), 2.87 (1H, dd, $J=14$, 8.5 Hz) and 3.13 (1H, dd, $J=14$, 3 Hz) (–CH$_2$CO–), 3.69 (3H, s, OCH$_3$), 3.96 (1H, m, >C$\underline{\mathrm{H}}$OH), 4.99 (2H, s, PhCH$_2$O–), 6.38 (1H, dd, $J=8$, 1 Hz, ArH), 6.50 (1H, dd, $J=8$, 1 Hz, ArH), 6.73, 7.01 (each 2H, d, $J=9.5$ Hz, ArH), 7.10—7.42 (6H, Ph-H and ArH). MS: 462 (M$^+$, 2), 121 (100). HRMS m/z (M$^+$): Calcd for $C_{29}H_{34}O_5$: 462.2407. Found: 462.2386.

1-(2-Benzyloxy-6-hydroxyphenyl)-3-hydroxy-9-(3,4-dimethoxyphenyl)nonan-1-one (**16c**): Pale yellow prisms (from hexane–ether), mp 73—75 °C. IR: 1625, 1600. ^{1}H-NMR: 1.00—1.76 (10H), 2.55 (2H, t, $J=8$ Hz, ArCH$_2$–), 2.95 (1H, dd, $J=18$, 8 Hz) and 3.18 (1H, dd, $J=18$, 3 Hz) (–CH$_2$CO–), 3.84, 3.86 (each 3H, s, 2×OCH$_3$), 4.04 (1H, m, >C$\underline{\mathrm{H}}$OH), 5.07 (2H, s, PhCH$_2$O–), 6.43 (1H, dd, $J=8$, 1 Hz, ArH), 6.56 (1H, dd, $J=8$, 1 Hz, ArH), 6.60—6.80 (3H, ArH), 7.16—7.44 (6H, Ph-H and ArH). MS: 492 (M$^+$, 4), 91 (100). HRMS m/z (M$^+$): Calcd for $C_{30}H_{36}O_6$: 492.2513. Found: 492.2517.

1-(2-Benzyloxy-6-hydroxyphenyl)-3-hydroxy-9-(3,4-methylenedioxyphenyl)nonan-1-one (**16d**): Pale yellow prisms (from benzene–ether), mp 89—90 °C. IR: 1619, 1594. ^{1}H-NMR: 1.00—1.88 (10H), 2.51 (2H, t, $J=7.8$ Hz, ArCH$_2$–), 2.90 (1H, br s, OH), 2.97 (1H, dd, $J=18.5$, 8.5 Hz) and 3.22 (1H, dd, $J=18.5$, 3 Hz) (–CH$_2$CO–), 4.02 (1H, m, >C$\underline{\mathrm{H}}$OH), 5.08 (2H, s, –OCH$_2$Ph), 5.89 (2H, s, –OCH$_2$O–), 6.42—6.77 (5H, ArH), 7.27—7.43 (6H, ArH and Ph-H), 13.03 (1H, s, OH). MS: 476 (M$^+$, 13), 91 (100). HRMS m/z (M$^+$): Calcd for $C_{29}H_{32}O_6$: 476.2200. Found: 476.2220.

1-(2-Hydroxy-6-methoxyphenyl)-3-hydroxy-9-(3,4-methylenedioxyphenyl)nonan-1-one (**16e**): Compound **16e** (100%) was prepared from **7d** and 6-hydroxy-2-methoxyacetophenone, as described for the corresponding benzyl ether, as pale yellow prisms (from hexane–ether), mp 85—86 °C. IR: 1619, 1595. ^{1}H-NMR: 1.16—1.80 (10H), 2.52 (2H, t, $J=7.5$ Hz, PhCH$_2$–), 3.05 (1H, dd, $J=18$, 8 Hz) and 3.29 (1H, dd, $J=18$, 4 Hz) (–CH$_2$CO–), 3.88 (3H, s, OCH$_3$), 4.12 (1H, m, C$\underline{\mathrm{H}}$OH), 5.89 (2H, s, –OCH$_2$O–), 6.39 (1H, d, $J=8$ Hz, ArH), 6.52—6.80 (3H, ArH), 6.54 (1H, d, $J=8$ Hz, ArH), 7.28 (1H, t, $J=8$ Hz, ArH). MS: 400 (M$^+$, 23), 135 (100). HRMS m/z (M$^+$): Calcd for $C_{23}H_{28}O_6$: 400.1886. Found: 400.1891.

1-(2,6-Dihydroxyphenyl)-3-hydroxy-9-(3,4-methylenedioxyphenyl)nonan-1-one (8) Compound **8** was prepared from **7d** and 2,6-dihydroxyacetophenone in the manner described for the preparation of the monobenzyl derivative with the use of 4 mol eq of LDA, in the yield of 38%, as a yellow oil. IR: 3350, 1641, 1625. ^{1}H-NMR: 1.12—1.80 (10H), 2.51 (2H, t, $J=7.8$ Hz, ArCH$_2$–), 3.06 (1H, dd, $J=12$, 4 Hz) and 3.40 (1H, dd, $J=12$, 9 Hz) (–CH$_2$CO–), 4.22 (1H, m, >C$\underline{\mathrm{H}}$OH), 5.90 (2H, s, –OCH$_2$O–), 6.40 (2H, d, $J=8$ Hz, ArH), 6.48—6.76 (3H, ArH), 7.30 (1H, t, $J=8$ Hz, ArH). MS: 386 (M$^+$, 1), 135 (100). HRMS m/z (M$^+$): Calcd for $C_{22}H_{26}O_6$: 386.1730. Found: 386.1723.

Dehydration of the Aldol 8 The aldol **8** (90 mg, 0.23 mmol) and *p*-TsOH

(5 mg, 0.02 mmol) in benzene (10 ml) were heated under reflux for 3.5 h, and the mixture was worked up as described below to give the chromanone **10** (58 mg, 66%) as a yellow oil. IR: 3200, 1627, 1600. ^{1}H-NMR: 1.12—1.92 (10H), 2.53 (2H, t, $J=7.6$ Hz, $ArCH_2-$), 2.68 (2H, m, $-CH_2CO-$), 4.28 (1H, m, $>CHO-$), 5.90 (2H, s, $-OCH_2O-$), 6.32—6.46 (2H, ArH), 6.48—6.78 (3H, ArH), 7.38 (1H, d, $J=8$ Hz, ArH). MS: 368 (M^+, 90), 163 (100). HRMS m/z (M^+): Calcd for $C_{22}H_{24}O_5$: 368.1624. Found: 368.1627.

Dehydration of the Aldols 16 (General Procedure) One of the aldols **16** (0.65 mmol) and p-TsOH (0.11 mmol) in benzene (10 ml) were heated under reflux for 1 h. The mixture was cooled, washed with saturated aqueous $NaHCO_3$, and concentrated. Chromatography of the residue gave the corresponding enone **17** in the yield indicated in Table III.

1-(2-Benzyloxy-6-hydroxyphenyl)-9-phenyl-2-nonen-1-one (**17a**): Yellow oil. IR: 1637, 1611, 1575. ^{1}H-NMR: 1.06—1.74 (8H), 2.02 (2H, m, $-C\underline{H}_2CH=$), 2.59 (2H, t, $J=7.5$ Hz, $PhCH_2-$), 5.08 (2H, s, $PhCH_2O-$), 6.52 (1H, dd, $J=8$, 1 Hz, ArH), 6.60 (1H, dd, $J=8$, 1 Hz, ArH), 6.78—7.46 (11H, ArH, Ph-H, and $-C\underline{H}=C\underline{H}CO-$). MS: 414 ($M^+$, 5), 91 (100). HRMS m/z (M^+): Calcd for $C_{28}H_{30}O_3$: 414.2196. Found: 414.2219.

1-(2-Benzyloxy-6-hydroxyphenyl)-9-(4-methoxyphenyl)-2-nonen-1-one (**17b**): Yellow oil. IR: 1637, 1609, 1575. ^{1}H-NMR: 0.98—1.62 (8H), 1.96 (2H, m, $-C\underline{H}_2CH=$), 2.45 (2H, t, $J=8$ Hz, $ArCH_2-$), 3.69 (3H, s, OCH_3), 5.01 (2H, s, $PhCH_2O-$), 6.39 (1H, dd, $J=8$, 1 Hz, ArH), 6.52 (1H, dd, $J=8$, 1 Hz, ArH), 6.73, 6.99 (each 2H, d, $J=8$ Hz, ArH), 7.00—7.42 (8H, ArH, Ph-H, and $-C\underline{H}=C\underline{H}CO-$). MS: 444 ($M^+$, 13), 91 (100). HRMS m/z (M^+): Calcd for $C_{29}H_{32}O_4$: 444.2266. Found: 444.2273.

1-(2-Benzyloxy-6-hydroxyphenyl)-9-(3,4-dimethoxyphenyl)-2-nonen-1-one (**17c**): Yellow prisms (from hexane–ether), mp 50—53 °C. IR : 1640, 1615, 1580. ^{1}H-NMR: 1.04—1.72 (8H), 2.04 (2H, m, $-C\underline{H}_2CH-$), 2.52 (2H, t, $J=8$ Hz, $ArCH_2-$), 3.84, 3.86 (each 3H, s, $2\times OCH_3$), 5.09 (2H, s, $PhCH_2-$), 6.44 (1H, d, $J=8$ Hz, ArH), 6.56 (1H, d, $J=8$ Hz, ArH), 6.62—6.88 (3H, ArH), 6.88—7.52 (8H, $-C\underline{H}=C\underline{H}CO-$, ArH, and Ph-H). MS: 474 (M^+, 38), 91 (100). HRMS m/z (M^+): Calcd for $C_{30}H_{34}O_5$: 474.2407. Found: 474.2401.

1-(2-Benzyloxy-6-hydroxyphenyl)-9-(3,4-methylenedioxyphenyl)-2-nonen-1-one (**17d**): Yellow oil. IR: 1639, 1611, 1576. ^{1}H-NMR: 1.12—1.72 (8H), 2.04 (2H, m, $-C\underline{H}_2CH=$), 2.51 (2H, t, $J=7.8$ Hz, $ArCH_2-$), 5.10 (2H, s, $PhCH_2O-$), 5.90 (2H, s, $-OCH_2O-$), 6.44 (1H, dd, $J=8$, 1 Hz, ArH), 6.56 (1H, dd, $J=8$, 1 Hz, ArH), 6.58—6.74 (3H, ArH), 6.80—7.50 (8H, ArH, Ph-H, and $-C\underline{H}=C\underline{H}CO-$). MS: 458 ($M^+$, 3), 91 (100). HRMS m/z (M^+): Calcd for $C_{29}H_{30}O_5$: 458.2029. Found: 458.2082.

1-(2-Hydroxy-6-methoxyphenyl)-9-(3,4-methylenedioxyphenyl)-2-nonen-1-one (**17e**): Yellow oil. IR: 1637, 1611, 1577. ^{1}H-NMR: 1.20—1.76 (8H), 2.28 (2H, m, $-CH_2CH=$), 2.52 (2H, t, $J=7.5$ Hz, $ArCH_2-$), 3.88 (3H, s, OCH_3), 5.90 (2H, s, $-OCH_2O-$), 6.52 (1H, dd, $J=8$, 1 Hz, ArH), 6.56 (1H, dd, $J=8$, 1 Hz, ArH), 6.56—6.74 (3H, ArH), 7.00 (1H, dt, $J=15$, 6 Hz, $-C\underline{H}=CHCO-$), 7.16 (1H, d, $J=15$ Hz, $-CH=C\underline{H}CO-$), 7.30 (1H, t, $J=8$ Hz, ArH). MS: 382 (M^+, 19), 177 (100). HRMS m/z (M^+): Calcd for $C_{23}H_{26}O_5$: 382.1781. Found: 382.1754.

Hydrogenation of the Enones 17 (General Procedure) A solution of an enone **17** (0.11 mmol) in acetone (20 ml) was hydrogenated over 10% Pd–C (50 mg) at room temperature under a hydrogen atmosphere at a pressure of 3.5 kg/cm^2 for 6 h. Removal of the catalyst and the solvent from the reaction mixture provided a residue, which was purified by chromatography to give **18** in the yield indicated in Table III.

1-(2,6-Dihydroxyphenyl)-9-phenylnonan-1-one (Malabaricone A) [**18a** (=**1a**)]: Pale yellow prisms (from hexane–ether), mp 78—80 °C (lit. 81—82 °C).$^{1a)}$ IR: 3350, 1626, 1599. ^{1}H-NMR: 1.06—1.82 (12H), 2.60 (2H, t, $J=7.5$ Hz, $PhCH_2-$), 3.12 (2H, d, $J=7.5$ Hz, $-CH_2CO-$), 6.37 (2H, d, $J=8$ Hz, ArH), 6.98—7.36 (6H, ArH and Ph-H), 9.78 (1H, br s, OH). MS: 326 (M^+, 21), 137 (100). *Anal.* Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.13; H, 8.27. The data were identical with these reported for malabaricone A.$^{1a)}$

1-(2,6-Dihydroxyphenyl)-9-(4-methoxyphenyl)nonan-1-one (**18b**): Yellow prisms (from hexane–ether), mp 78—80 °C. IR: 3300, 1626, 1605. ^{1}H-NMR: 1.08—1.80 (12H), 2.52 (2H, t, $J=7.5$ Hz, $ArCH_2-$), 3.10 (2H, t, $J=8$ Hz, $-CH_2CO-$), 3.76 (3H, s, OCH_3), 6.34 (2H, d, $J=8$ Hz, ArH), 6.78, 7.04 (each 2H, d, $J=8$ Hz, ArH), 7.20 (1H, t, $J=8$ Hz, ArH). MS: 356 (M^+, 46), 121 (100). HRMS m/z (M^+): Calcd for $C_{22}H_{28}O_4$: 356.1988. Found: 356.1986.

1-(2,6-Dihydroxyphenyl)-9-(3,4-dimethoxyphenyl)nonan-1-one (**18c**): Pale yellow prisms (from benzene), mp 128—130 °C. IR: 3300, 1635, 1605. ^{1}H-NMR: 1.12—1.88 (12H), 2.55 (2H, t, $J=7.5$ Hz, $ArCH_2-$), 3.15 (2H, t, $J=7.5$ Hz, $-CH_2CO-$), 3.83, 3.85 (each 3H, s, $2\times OCH_3$), 6.38 (2H, d, $J=8$ Hz, ArH), 6.56—6.86 (3H, ArH), 7.16 (1H, t, $J=8$ Hz, ArH). MS: 386 (M^+, 79), 151 (100). HRMS m/z (M^+): Calcd for $C_{23}H_{30}O_5$: 386.2094. Found: 386.2096.

1-(2,6-Dihydroxyphenyl)-9-(3,4-methylenedioxyphenyl)nonan-1-one (Malabaricone D) [**18d** (=**1d**)]: Yellow prisms (from benzene–hexane), mp 90.5—92 °C (lit. 90—91 °C).$^{1a)}$ UV: 225 (16300), 274 (13300), 345 (2600). IR ($CDCl_4$): 3591, 1633, 1605. ^{1}H-NMR: 1.08—1.88 (12H), 2.52 (2H, t, $J=7.6$ Hz, $ArCH_2-$), 3.12 (2H, t, $J=7.6$ Hz, $-CH_2CO-$), 5.90 (2H, s, $-OCH_2O-$), 6.37 (2H, d, $J=8$ Hz, ArH), 6.56—6.78 (3H, ArH), 7.21 (1H, t, $J=8$ Hz, ArH), 9.50 (2H, s, OH). MS: 370 (M^+, 100). *Anal.* Calcd for $C_{22}H_{26}O_5$: C, 71.35; H, 7.00. Found: C, 71.08; H, 7.17. The data were identical with those reported for malabaricone D.$^{1a)}$

1-(2-Hydroxy-6-methoxyphenyl)-9-(3,4-methylenedioxyphenyl)-nonan-1-one [(**18e** (=**1f**)]: Pale yellow prisms (from chloroform–methanol), mp 52—53 °C (lit. 51—52 °C).$^{1c)}$ IR: 1619, 1595. ^{1}H-NMR: 1.12—1.88 (12H), 2.52 (2H, t, $J=7.5$ Hz, $ArCH_2-$), 3.03 (2H, t, $J=7.5$ Hz, $-CH_2CO-$), 3.88 (3H, s, OCH_3), 5.90 (2H, s, $-OCH_2O-$), 6.38 (1H, dd, $J=8$, 1 Hz, ArH), 6.58 (1H, dd, $J=8$, 1 Hz, ArH), 6.56—6.80 (3H, ArH), 7.32 (1H, t, $J=8$ Hz, ArH). MS: 384 (M^+, 63), 151 (100). *Anal.* Calcd for $C_{23}H_{29}O_5$: C, 71.85; H, 7.34. Found: C, 71.41; H, 7.59. The data were identical with those reported for the corresponding natural product by Kumar *et al.*$^{1c)}$

1-(2,6-Dihydroxyphenyl)-9-(4-hydroxyphenyl)nonan-1-one (Malabaricone B) (1b) Boron tribromide (110 mg, 0.44 mmol) was added to a stirred solution of **18b** (27 mg, 0.078 mmol) in CH_2Cl_2 (8 ml) at 0 °C, and the mixture was allowed to warm to room temperature, then stirred for 20 min, poured into ice-water and extracted with AcOEt. Chromatography of the residue obtained by evaporation of the extract gave **1b** (25 mg, 96%) as pale yellow prisms (from benzene), mp 102—104 °C (lit. 102 °C).$^{1a)}$ IR: 3300 br, 1626, 1604. ^{1}H-NMR: 1.00—1.88 (12H), 2.51 (2H, t, $J=7$ Hz, $ArCH_2-$), 3.15 (2H, t, $J=7$ Hz, $-COCH_2-$), 6.36 (2H, d, $J=8$ Hz, ArH), 6.68, 7.00 (each 2H, d, $J=8$ Hz, ArH), 7.19 (1H, t, $J=8$ Hz, ArH). MS: 342 (M^+, 40), 137 (100). *Anal.* Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.48; H, 7.75. The data were identical with those reported for malabaricone B.$^{1a)}$

1-(2,6-Dihydroxyphenyl)-9-(3,4-dihydroxyphenyl)nonan-1-one (Malabaricone C) (1c) Boron tribromide (93 mg, 0.37 mmol) was added to a stirred solution of **18c** (20 mg, 0.052 mmol) in CH_2Cl_2 (7 ml), at 0 °C, and the mixture was allowed to warm to room temperature, then stirred for 10 min, poured into ice-water and extracted with AcOEt. The organic layer was washed, dried, and passed through a column of polyamide (Woelm, for thin layer chromatography), then the column was washed with the same solvent. Elution of the column with methanol yielded a crude product which was purified by chromatography on a Sephadex LH-20 (Pharmacia Fine Chemical) column with methanol to give **1c** (18 mg, 97%) as pale yellow prisms from benzene, mp 119—121 °C (lit. 125—126 °C).$^{1d)}$ IR: 1631, 1607. ^{1}H-NMR ($CDCl_3+CD_3OD$): 1.08—1.88 (12H), 2.46 (2H, t, $J=7.5$ Hz, $ArCH_2-$), 3.13 (2H, t, $J=7.5$ Hz, $-COCH_2-$), 6.35 (2H, d, $J=8$ Hz, ArH), 6.46 (1H, dd, $J=8$, 1.5 Hz, ArH), 6.60 (1H, d, $J=1.5$ Hz, ArH), 6.66 (1H, d, $J=8$ Hz, ArH), 7.16 (1H, t, $J=8$ Hz, ArH). MS: 358 (M^+, 66), 137 (100). *Anal.* Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.54; H, 7.54. This was identical with malabaricone C as confirmed by direct comparisons with an authentic sample.$^{1d)}$

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