Synthesis and Nematocidal Activity of Diarylnonanoids Related to Malabaricones[1)]

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Twenty diarylnonanones were synthesized and their nematocidal activity was examined. Among those, the *p*-hydroxy compound 16 exhibited the strongest activity comparable to the natural diarylnonanoids, malabaricones A and C. Diarylundecanoid 57 also showed appreciable activity.

Key words diarylnonanoid; diarylundecanoid; nematocidal activity; *Toxocara canis*; malabaricone; structure–activity relationship

Myristicaceous plants characteristically contain a rare class of natural products called diarylnonanoids which have nine carbon units between two aromatic rings.[3)] Malabaricones A—D[3a)] (Table 1) are typical examples, whose synthesis already has been achieved.[4)] In a previous paper,[5)] we showed that malabaricone C, a constituent of the arils of *Myristica fragrans*, had very strong nematocidal activity against the larva of *Toxocara canis*. However, the compound was very unstable to air oxidation: the activity was instantly diminished when the compound was exposed to sodium hydroxide. We therefore searched for synthetic diarylnonanoids which were stable to air oxidation and share comparable activity with malabaricone C. At the same time, the diarylundecanoid **57** was an another synthetic target, but, although this compound was reported as the only natural product of the diarylundecane structure in a South-American Myristicaceous plant, *Virola sebifera*,[6)] synthetic proof of the structure has not been available.

Results and Discussion

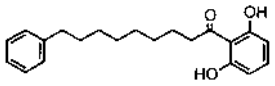
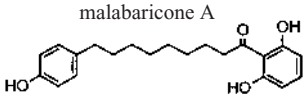
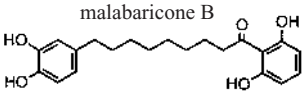
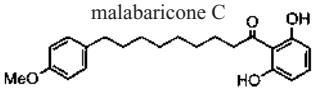
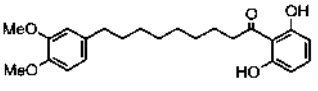
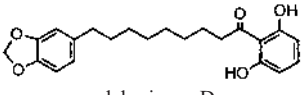
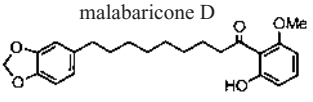
Nematocidal Activity First, the nematocidal activity of natural malabaricones and their analogs (**1**—**7**),[4)] all of which have a 2,6-dihydroxyacetophenone moiety at one terminus, against second-stage larvae of *Toxocara canis* was tested (Table 1).[7)] Those compounds which have phenolic hydroxyl(s) at the other terminus (**2**, **3**) were active, while those in which the hydroxyl group was masked (**5**, **6**) were inactive or very weakly active. However, rather unexpectedly, malabaricone A (**1**) and compound **4** showed very strong activities: particularly, the activity of **1** was almost equal to or stronger than that of malabaricone C (**3**), suggesting that the presence of a phenolic group at both termini is not necessarily required.

Therefore, one terminus was fixed to the phenyl group as in malabaricone A (**1**), and the other acetophenone terminus was varied. The results (Table 2) indicated that at least one phenolic group is necessary at the acetophenone terminus, since the non-phenolic compounds (**8**—**12**) were almost completely ineffective. *o*-Hydroxy derivatives (**13**, **14**) were inactive, since in these compounds the hydroxy group is masked by a strong chelation with the carbonyl group. For this reason, compounds **17** and **18** as well as **1** behave as mono-phenolic compounds and all of them showed comparable activities. Interestingly, the *p*-hydroxy compound **16** showed very strong activity (minimal lethal concentration (MLC)=8 μM) which was almost equal to that of malabaricone A, whereas the activity of the *m*-hydroxy compound (**15**) was weaker. Introduction of a further hydroxy group to **15** at the 4′ position (*i.e.* compound **19**) increased the activity.

Next, fixing the acetophenone moiety as the *p*-hydroxy derivative, the other terminus was changed to *p*-methoxyphenyl and 3,4-dimethoxyphenyl groups (**21** and **23**). The results indicated that the introduction of electron releasing group(s) (OMe) at the other terminus greatly reduced the activity, suggesting that a suitable balance of electron density at the two termini is neccessary. In fact, a reduction of the carbonyl group, as in **51**, regenerated the activity, though very weakly, while **23** and **52** were completely inactive.

The structure–activity relationship concerning the chain

Table 1. Minimal Lethal Concentration (MLC) of Malabaricones against *T. canis* (μM, 24 h)

	Compound	MLC
1	 malabaricone A	5
2	 malabaricone B	25
3	 malabaricone C	6—10
4		20
5		100—300
6	 malabaricone D	>300
7		>300

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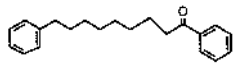
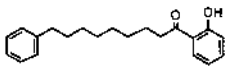
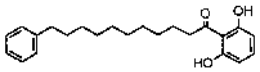
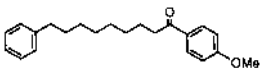
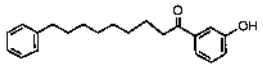
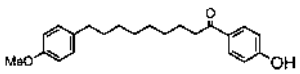
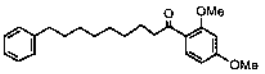
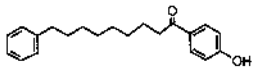
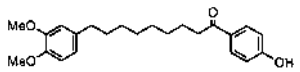
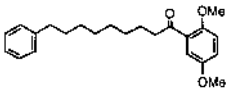
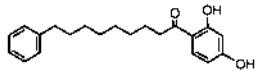
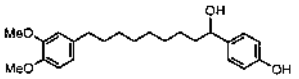
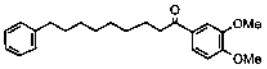
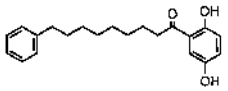
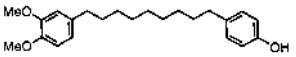
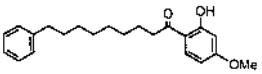
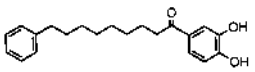
length between the two aromatic rings is another point of interest for investigation, since it is known that the nematocidal activity of piperamides largely depends on the length of side chains.[8] The activity of diarylundecanoid **57** was fairly strong but slightly weaker than that of malabaricone A (**1**), suggesting that a suitable middle chain length is necessary for the high nematocidal activity, and the compound of the strongest activity will be found in diarylnonanoids, since the activity of some of the above compounds were stronger than that of diarylheptanoids such as curcuminoids.[9]

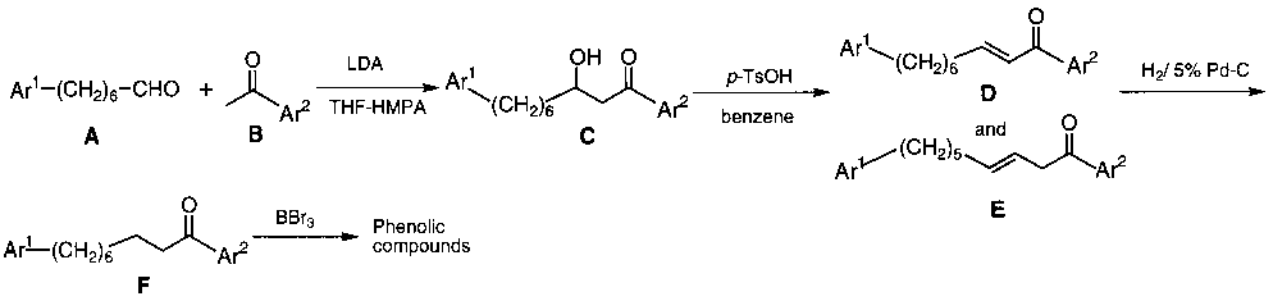
In conclusion, the *p*-hydroxy compound **16**,which is fairly stable to air oxidation, is the strongest synthetic nematocidal compound.

Synthesis Synthesis of the above compounds was done as reported for malabaricones.[4] Arylheptanals (A)[10] were reacted with acetophenones (B) in the presence of lithium diisopropylamide (LDA) in tetrahydrofuran (THF)–hexamethylphosphoric triamide (HMPA) at −78 °C to give hydroxyketones (C), usually in 72—77% yield for the protected compounds. Elevating the reaction temperature caused a retro-aldol reaction, thus decreasing the yields. Hydroxyacetophenones can also be used without the protection of phenolic hydroxy groups, when an excess molar amount of LDA corresponding to the number of hydroxy group(s) was em-

Table 2. MLC of Diarylnonanones and a Diarylundecanone (**57**) against *T. canis* (μM, 24 h)

No.	Compound	MLC	No.	Compound	MLC	No.	Compound	MLC
8		>300	**14**		>300	**57**		40
9		>300	**15**		130	**21**		—
10		>300	**16**		8	**23**		>1000
11		>300	**17**		25	**51**		500—750
12		>300	**18**		30	**52**		>1000
13		>1000	**19**		50			

—: not tested.



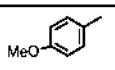
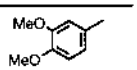
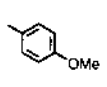
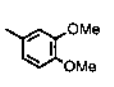
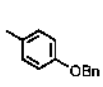
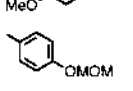
Ar^1	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph		
Ar^2	Ph												
C	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**-**	**-**	**33**	**34**
D	**35**	**37**	**38**	**39**	**41**	**42**	**43**	**45**	**-**	**-**	**-**	**46**	**47**
E	**36**	**-**	**-**	**40**	**-**	**-**	**44**	**-**	**-**	**-**	**-**	**-**	**-**
F	**8**	**9**	**10**	**11**	**12**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**22**

Chart 1

ployed, but the yield was usually low (*ca*. 10%) except in the case of *o*-hydroxyacetophenone, which gave the expected product in *ca*. 70%. This may be due to the fact that the phenolic character of the hydroxyl group has been lost by chelation to the *o*-carbonyl group. The aldol products were dehydrated with *p*-TsOH to the α,β-unsaturated ketones (D) which were sometimes accompanied with β,γ-unsaturated ketones (E). Both of them were hydrogenated over 5—10% Pd–C in acetone to the same saturated ketones (F). *O*-Methyl derivatives were demethylated with BBr_3, if necessary. Demethylation took place first at the *O*-methyl group *ortho* to the carbonyl (like **10**→**13**→**17**), as expected.[11] Demethylation of 1-(4-methoxyphenyl)-9-phenylnonan-1-one (**9**) to the *p*-hydroxy derivative **16** gave a poor result, though the reason is obscure. Therefore, a direct aldol reaction of phenylheptanal with *p*-hydroxyacetophenone has value for the synthesis of **16**, though the yield was low (10%). 1-Aryl-9-phenylnonan-1-ones **8**—**19** were thus synthesized.

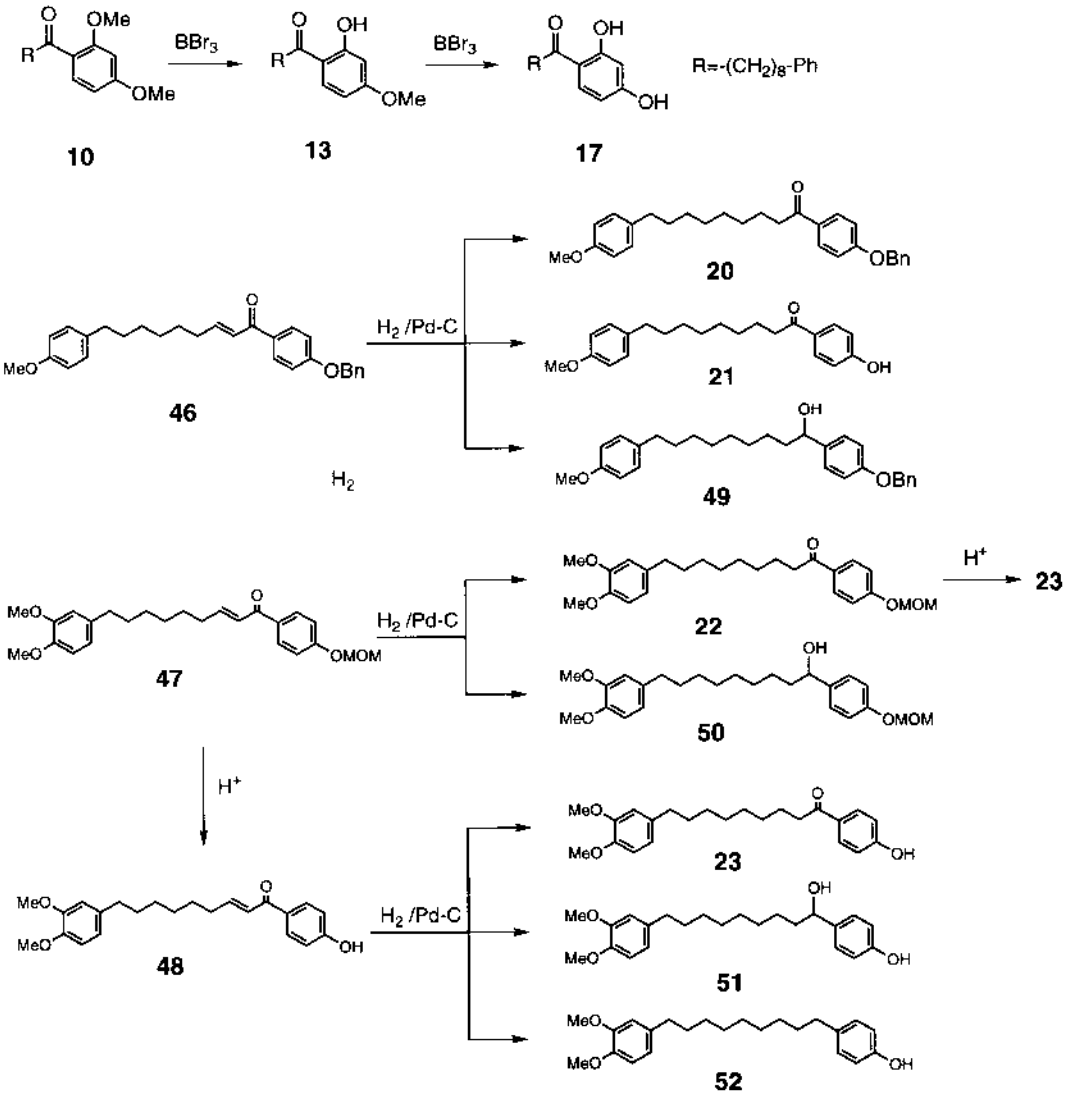


Chart 2

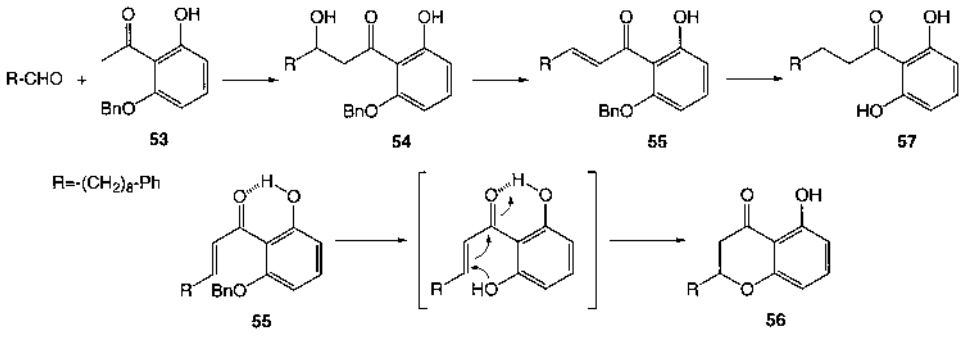


Chart 3

Table 3. Comparison of Synthetic and Natural Diarylundecanoid (**57**)

	Synthetic[a]	Natural[b]
Crystallization	Needles from ether–hexane	Crystals from MeOH
mp	76—77 °C	69—71 °C
^{1}H-NMR	500 MHz ($CDCl_3$)	60 MHz (CCl_4)
	9.81 (br s, 2×OH)	9.7 (s, 2×OH)
	7.20 (1H, t, J=8.5 Hz, H-4′)	7.23 (t, J=8 Hz, H-4′)
	7.14—7.29 (5H, m, PhH)	7.0—7.3 (m, Ph-H)
	6.38 (2H, d, J=8.5 Hz, H-3′, 5′)	6.33 (2H, d, J=8 Hz, H-3′, 5′)
	3.12 (1H, t, J=7.8 Hz, H-2)	3.10 (1H, t, J=7 Hz, H-2)
	2.59 (1H, t, J=8.0 Hz, H-11)	2.58 (1H, t, J=7 Hz, H-11)
	1.69 (2H, quintet, J=8.0 Hz, H-10)	
	1.60 (2H, quintet, J=7.8 Hz, H-3)	1.30 (16H, br s, 8×CH_2)
	1.25—1.40 (12H, m, 6×CH_2)	
IR	KBr	Film
	3260, 1634, 1587, 1504, 1453,	3280, 1620, 1590, 1500, 1450,
	1365, 1333, 1256, 1204	1370, 1340, 1250, 1200
MS m/z	354 (M^+, 73), 336 (50), 189 (34),	354 (M^+, 11), 336 (14),326 (14),[c]
	175 (13), 165 (76), 152 (70),	189 (13), 175 (4), 165 (31),
	147 (8), 138 (20), 137 (100),	152 (31), 147 (4), 138 (11),
	123 (11), 91 (72)	137 (100), 123 (13), 91 (17)

a) Present work. *b*) See ref. 6. *c*) This peak was not found in the synthetic compound. It may be due to the contamination of malabaricone A.

Compounds **21** and **23** which have a methoxy or dimethoxy group at the other terminus were synthesized analogously. However, the hydrogenation step in the synthesis of these compounds always accompanied side reactions (Chart 2).

For the synthesis of diarylundecanoid **57**, phenylnonanal[10] was reacted with 2-benzyloxy-6-hydroxyacetophenone (**53**), and the product **54** was dehydrated to give an α,β-unsaturated ketone **55**, which was contaminated with a cyclic ketone **56**, the product due to debezylation followed by cyclization as shown in Chart 3. Hydrogenation of the double bond in **55** and hydrogenolysis of the benzyl group at the same time gave the expected product **57**. Although a sample of the natural product was not available, comparisons of its spectral data with those reported[6] for the natural product strongly suggested that they are identical (Table 3).

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanaco melting point apparatus and are uncorrected. IR spectra were taken for $CHCl_3$ solutions on a JASCO A-202 or a Shimadzu IR-460 and the data are given in cm^{-1}. NMR spectra were measured on a JEOL FX-100 (100 MHz for ^{1}H) or a JEOL GSX-500 (500 MHz for ^{1}H) spectrometer in $CDCl_3$ solutions with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. Mass spectra (MS) were taken with a Hitachi M-80 machine at 70 eV, and M^+ and major peaks (more than 10% of the base peak) are indicated as m/z (%). All new compounds gave satisfactory high-resolution MS (HRMS) data. Column chromatography was performed on silica gel (Wako-gel C-200). For TLC, Merck pre-coated plates GF_{254} were used and spots were developed by spraying 5% H_2SO_4 and heating the plates until coloration took place. All organic extracts were washed with brine and dried over anhydrous Na_2SO_4 before concentration.

Aldol Condensation of 9-Arylheptanal (A) with Acetophenone (B) (General Procedure) For Protected Acetophenones: LDA in THF was prepared by the addition of 1.36 M *n*-BuLi (1.2 eq) in hexane to diisopropylamine (1.4 eq) in THF (3—5 ml) at −78 °C, followed by stirring for 15 min at 0 °C. An acetophenone (B, 1.1 eq) in THF (6—10 ml) was added to this solution at −78 °C and stirred for 1 h to prepare the enolate. A solution of 9-arylheptanal (A, 1 eq) and HMPA (2.4 mol eq) in THF (6—10 ml) was added to the enolate and the mixture was stirred for 1 h. The reaction was quenched with diluted HCl and ice. Extraction of the mixture with ether and chromatography of the product gave 1,9-diaryl-3-hydroxynonan-1-one (C).

For Hydroxyacetophenones: The following molar ratios of reagents were used to arylheptanal (1.0 mol eq) and an acetophenone (1.1 mol eq). Monohydroxyacetophenones: diisopropylamine (2.6 eq), *n*-BuLi (2.2 eq), and HMPA (4.4 eq). Dihydroxyacetophenones: diisopropylamine (3.8 eq), *n*-BuLi (3.6 eq), and HMPA (7.2 eq).

1,9-Diphenyl-3-hydroxynonan-1-one (**24**): Yield (Y), 77%. Colorless solid, mp 34—35 °C. IR: 3540, 1677. ^{1}H-NMR: 7.94 (2H, dd, J=8, 1.8 Hz, H-2′, 6′), 7.64—7.30 (3H, m, H-3′, 4′, 5′), 7.26—7.00 (5H, m, PhH), 4.13 (1H, m, H-3), 3.20 (1H, dd, J=18, 4 Hz, H-2), 2.96 (1H, dd, J=18, 8 Hz, H-2), 2.61 (2H, t, J=7 Hz, H-9), 1.78—1.10 (10H, m, H-4—8). MS: 310 (M^+, 2), 120 (22), 105 (100).

1-(4-Methoxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**25**): Y, 70%. Pale yellow oil. IR: 3515, 1670. ^{1}H-NMR (500 MHz): 7.92 (2H, d, J=9.0 Hz, H-2′, 6′), 7.29—7.14 (5H, m, PhH), 6.93 (2H, d, J=9.0 Hz, H-3′, 5′), 4.18 (1H, m, H-3), 3.86 (3H, s, OMe), 3.40 (1H, br s, OH), 3.10 (1H, dd, J=17.5, 2.8 Hz, H-2), 2.95 (1H, dd, J=17.5, 9.5 Hz, H-2), 2.60 (2H, t, J=7.7 Hz, H-9), 1.66—1.32 (10H, m, H-4—8). MS: 340 (M^+, 6), 190 (28), 150 (70), 135 (96), 104 (47), 91 (100).

1-(2,4-Dimethoxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**26**): Y, 69%. Pale yellow oil. IR: 3535, 1652. ^{1}H-NMR (500 MHz): 7.84 (1H, d, J=8.7 Hz, H-6′), 7.29—7.14 (5H, m, PhH), 6.53 (1H, dd, J=8.7, 2.5 Hz, H-5′), 6.45 (1H, d, J=2.5 Hz, H-3′), 4.13 (1H, m, H-3), 3.88, 3.85 (each 3H, s, OMe), 3.42 (1H, br s, OH), 3.20 (1H, dd, J=18.0, 2.5 Hz, H-2), 2.95 (1H, dd, J=18.0, 9.2 Hz, H-2), 2.60 (2H, t, J=8.0 Hz, H-9), 1.66—1.31 (10H, m, H-4—8). MS: 370 (M^+, 2), 190 (33), 180 (56), 166 (27), 165 (98), 122 (23), 105 (22), 104 (66), 92 (55), 91 (100).

1-(2,5-Dimethoxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**27**): Y, 72%. Pale yellow oil. IR: 3550, 1661. ^{1}H-NMR (500 MHz): 7.28 (1H, d, J=3.2 Hz, H-6′), 7.27—7.14 (5H, m, PhH), 7.04 (1H, dd, J=9.0, 3.2 Hz, H-4′), 6.90 (1H, d, J=9.0 Hz, H-3′), 4.14 (1H, m, H-3), 3.85, 3.78 (each 3H, s, OMe), 3.23 (1H, dd, J=18.0, 2.4 Hz, H-2), 3.22 (1H, br s, OH), 3.01 (1H, dd, J=18.0, 9.2 Hz, H-2), 2.60 (2H, t, J=7.7 Hz, H-9), 1.75—1.30 (10H, m, H-4—8). MS: 370 (M^+, 7), 180 (39), 165 (100).

1-(3,4-Dimethoxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**28**): Y, 75%. Pale yellow prisms from benzene–methanol, mp 78—79 °C. IR: 3500, 1665. ^{1}H-NMR: 7.60—7.40 (2H, m, ArH), 7.24—7.00 (5H, m, PhH), 6.82 (1H, d, J=8 Hz, ArH), 4.12 (1H, m, H-3), 3.92 (6H, s, 2×OMe), 3.08—2.88 (2H, m, H-2), 2.58 (2H, t, J=7 Hz, H-9), 1.84—1.16 (10H, m, H-4—8). MS: 370 (M^+, 1), 180 (22), 165 (64), 104 (50), 92 (50), 91 (100).

1-(2-Hydoxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**29**): Y, 74%. Pale yellow oil. IR: 3580, 1636. ^{1}H-NMR: 12.1 (1H, s, OH), 7.80—6.72 (9H, m, ArH, PhH), 4.08 (1H, m, H-3), 3.20—3.00 (2H, m, H-2), 2.60 (2H, t, J=7 Hz, H-9), 1.80—1.12 (10H, m, H-4—8). MS: 326 (M^+, 1), 190 (23), 147 (38), 136 (51), 121 (100).

1-(3-Hydoxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**30**): Y, 18%. Yellow oil. IR: 3320, 1671. ^{1}H-NMR: 7.44—6.88 (9H, m, ArH, PhH), 4.14 (1H, m, H-3), 3.08—2.86 (2H, m, H-2), 2.56 (2H, t, J=7 Hz, H-9), 1.76—1.04 (10H, m, H-4—8). MS: 326 (M^+, 1), 136 (60), 121 (100).

1-(4-Hydoxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**31**): Y, 16%. Colorless prisms from hexane–benzene, mp 83—85 °C. IR: 3250, 1661. ^{1}H-NMR: 7.76 (2H, d, J=8 Hz, H-2′, 6′), 7.40—6.88 (5H, m, PhH), 6.80 (2H, d, J=8 Hz, H-3′, 5′), 4.16 (1H, m, H-3), 3.08—2.84 (2H, m, H-2), 2.56 (2H, t, J=7.5 Hz, H-9), 1.72—1.00 (10H, m, H-4—8). MS: 326 (M^+, 11), 165 (31), 136 (60), 121 (100).

1-(2,4-Hydoxyphenyl)-3-hydroxy-9-phenylnonan-1-one (**32**): Y, 10%. Yellow oil. IR: 3210, 1633. ^{1}H-NMR: 7.48 (1H, d, J=7 Hz, H-6′), 7.36—6.96 (5H, m, PhH), 6.32 (2H, m, H-3′, 5′), 4.12 (1H, m, H-3), 3.08—2.90 (2H, m, H-2), 2.58 (2H, t, J=7 Hz, H-9), 1.80—1.04 (10H, m, H-4—8). MS: 342 (M^+, 2), 190 (23), 163 (132), 144 (32), 137 (100).

1-(4-Benzyloxyphenyl)-3-hydroxy-9-(4-methoxyphenyl)nonan-1-one (**33**): Y, 23%. Colorless solid, mp <30 °C. IR: 1666. ^{1}H-NMR (500 MHz): 7.93, 7.01 (each 2H, d, J=9.0 Hz, H-3′, 5′, H-2′, 6′), 7.44—7.33 (5H, m, PhH), 7.09, 6.82 (each 2H, d, J=8.3 Hz, H-2″, 6″, H-3″, 5″), 5.14 (2H, s, PhC$\underline{H}_2$), 4.18 (1H, m, H-3), 3.78 (3H, s, OMe), 3.11 (1H, dd, J=17.3, 2.4 Hz, H-2), 2.95 (1H, dd, J=17.3, 8.7 Hz, H-2), 2.54 (2H, t, J=7.5 Hz, H-9), 1.63—1.31 (10H, m, H-4—8). MS: 446 (M^+, 2), 121 (100), 91 (100).

1-(4-Methoxymethoxyphenyl)-3-hydroxy-9-(3,4-dimethoxyphenyl)nonan-1-one (**34**): Y, 36%. Colorless oil. IR: 1669. ^{1}H-NMR (500 MHz): 7.92 (2H, d, J=8.8 Hz, H-2″, 6″), 7.08 (2H, d, J=8.8 Hz, H-3″, 5″), 6.78 (1H, d, J=8.8 Hz, H-6′), 6.71 (1H, br d, J=8.3 Hz, H-5′), 6.70 (1H, br s, H-2′), 5.25 (2H, s, OCH_2O), 4.19 (1H, m, H-3), 3.87, 3.85, 3.48 (each 3H, s, OMe), 3.35

(1H, d, J=3.4 Hz, OH), 3.12 (1H, dd, J=17.3, 2.6 Hz, H-2), 2.97 (1H, dd, J=17.3, 9.3 Hz, H-2), 2.55 (2H, t, J=8.0 Hz, H-9), 1.65—1.30 (10H, m, H-4—8). MS: 430 (M^+, 6), 251 (32), 250 (100).

Dehydration of 1,9-Diaryl-3-hydroxynonan-1-one (C) to the 2-Ene (D) (General Procedure) A mixture of the 3-hydroxynonan-1-one (C) (0.15—0.6 g) and *p*-TsOH (0.2 eq) in benzene (20—40 ml) was heated under reflux for 0.5—2 h with occasional monitoring by TLC. The mixture was poured into cold water and extracted with ether, which was washed with a saturated $NaHCO_3$ solution, and concentrated to give the 2-ene (D). This was contaminated, in most cases, with the 3-ene (E), which could be separated by careful chromatography.

1,9-Diphenyl-2-nonen-1-one (**35**): Y, 62%. Pale yellow oil. IR: 1668. ^{1}H-NMR: 7.90 (2H, dd, J=8, 2 Hz, H-2′, 6′), 7.52—7.36 (3H, m, H-3′, 4′, 5′), 7.24—7.04 (5H, m, PhH), 7.04 (1H, dt, J=16, 7 Hz, H-3), 6.82 (1H, d, J=16 Hz, H-2), 2.58 (2H, t, J=7 Hz, H-9), 2.26 (2H, q, J=7 Hz, H-4), 1.68—1.24 (8H, m, H-5—8). MS: 292 (M^+, 4), 159 (22), 105 (75), 91 (100).

1,9-Diphenyl-3-nonen-1-one (**36**): Y, 19%. Pale yellow oil. IR: 1685. ^{1}H-NMR: 7.92 (2H, dd, J=8, 2 Hz, H-2′, 6′), 7.32—7.00 (8H, m, H-3′, 4′, 5′, PhH), 5.64—5.08 (2H, m, H-3, 4), 3.72—3.56 (2H, m, H-2), 2.56 (2H, t, J=7.5 Hz, H-9), 2.12—1.88 (2H, m, H-5), 1.84—1.20 (6H, m, H-6, 7, 8). MS: 292 (M^+, 1), 105 (100).

1-(4-Methoxyphenyl)-9-phenyl-2-nonen-1-one (**37**): Y, 100% (contaminated with the 3-ene). Yellow oil. IR: 1665. ^{1}H-NMR (500 MHz): 7.94 (2H, d, J=9.0 Hz, H-2′, 6′), 7.29—7.14 (5H, m, PhH), 7.04 (1H, dt, J=15.5, 7.5 Hz, H-3), 6.94 (2H, d, J=9.0 Hz, H-3′, 5′), 6.87 (1H, dt, J=15.5, 1.0 Hz, H-2), 3.86 (3H, s, OMe), 2.60 (2H, t, J=8.0 Hz, H-9), 2.29 (2H, qd, J=7.5, 1.0 Hz, H-4), 1.66—1.32 (8H, m, H-5—8). MS: 322 (M^+, 54), 189 (45), 150 (42), 135 (100).

1-(2,4-Dimethoxyphenyl)-9-phenyl-2-nonen-1-one (**38**): Y, 92% (contaminated with the 3-ene). Yellow oil. IR: 1656. ^{1}H-NMR (500 MHz): 7.64 (1H, d, J=8.5 Hz, H-6′), 7.30—7.14 (5H, m, PhH), 6.90 (1H, dt, J=15.5, 7.0 Hz, H-3), 6.78 (1H, dt, J=15.5, 1.0 Hz, H-2), 6.52 (1H, dd, J=8.5, 2.3 Hz, H-5′), 6.46 (1H, d, J=2.3 Hz, H-3′), 3.84 (2×3H, s, OMe), 2.60 (2H, t, J=7.8 Hz, H-9), 2.24 (2H, qd, J=7.0, 1.0 Hz, H-4), 1.66—1.30 (8H, m, H-5—8). MS: 352 (M^+, 61), 219 (51), 191 (36), 166 (30), 165 (100).

1-(2,5-Dimethoxyphenyl)-9-phenyl-2-nonen-1-one (**39**): Y, 73%. Yellow oil. IR: 1657. ^{1}H-NMR (500 MHz): 7.29—7.14 (5H, m, PhH), 7.06 (1H, d, J=3.0 Hz, H-6′), 6.97 (1H, dd, J=9.0, 3.0 Hz, H-4′), 6.89 (1H, d, J=9.0 Hz, H-3′), 6.87 (1H, dt, J=15.0, 7.0 Hz, H-3), 6.68 (1H, dt, J=15.0, 1.5 Hz, H-2), 3.79, 3.77 (each 3H, s, OMe), 2.60 (2H, t, J=7.7 Hz, H-9), 2.25 (2H, qd, J=7.0, 1.5 Hz, H-4), 1.67—1.30 (8H, m, H-5—8). MS: 352 (M^+, 81), 191 (23),180 (15), 165 (100).

1-(2,5-Dimethoxyphenyl)-9-phenyl-3-nonen-1-one (**40**: *E*/*Z*=7/1 Mixture): Y, 22%. Yellow oil. IR: 1663. ^{1}H-NMR (500 MHz): *E*-Isomer: 7.28—7.14 (6H, m, H-6′, PhH), 7.08 (1H, dd, J=9.3, 3.4 Hz, H-4′), 6.89 (1H, d, J=9.3 Hz, H-3′), 5.64 (1H, dt, J=15.2, 6.8 Hz, H-4), 5.52 (1H, dt, J=15.2, 6.8 Hz, H-3), 3.85, 3.78 (each 3H, s, OMe), 3.69 (2H, dd, J=6.8, 1.0 Hz, H-2), 2.58 (2H, t, J=7.8 Hz, H-9), 2.03 (2H, td, J=7.3, 6.8 Hz, H-5), 1.65—1.25 (6H, m, H-6, 7, 8). *Z*-Isomer: 6.73 (1H, d, J=11.5 Hz, H-4), 6.17 (1H, td, J=11.5, 7.2 Hz, H-4). Other protons could not be assigned due to overlapping with other signals. MS: 352 (M^+, 64), 166 (64), 165 (100).

1-(3,4-Dimethoxyphenyl)-9-phenyl-2-nonen-1-one (**41**): Y, 98%. Pale yellow prisms from benzene–methanol, mp 48—49 °C. IR: 1664. ^{1}H-NMR: 7.60—6.68 (10H, m, H-2′, 5′, 6′, 2, 3, PhH), 3.92 (2×3H, s, OMe), 2.58 (2H, t, J=7 Hz, H-9), 2.28 (2H, q, J=7 Hz, H-4), 1.76—1.16 (8H, m, H-5—8). MS: 352 (M^+, 10), 180 (24), 165 (100).

1-(2-Hydoxyphenyl)-9-phenyl-2-nonen-1-one (**42**): Y, 88%. Yellow solid, mp 30—32 °C. IR: 1649. ^{1}H-NMR: 12.7 (1H, s, OH), 7.88—6.72 (11H, m, H-2, 3, ArH, PhH), 2.60 (2H, t, J=7 Hz, H-9), 2.32 (2H, q, J=7 Hz, H-4), 1.80—1.20 (8H, m, H-5—8). MS: 308 (M^+, 18), 148 (35), 147 (100).

1-(3-Hydoxyphenyl)-9-phenyl-2-nonen-1-one (**43**): Y, 83% (contaminated with the 3-ene **44**). Yellow oil. IR: 1662. ^{1}H-NMR: 7.60—7.06 (9H, m, ArH, PhH), 7.06 (1H, dt, J=16, 6 Hz, H-3), 6.78 (1H, d, J=16 Hz, H-2), 2.60 (2H, t, J=6 Hz, H-9), 2.24 (2H, q, J=6 Hz, H-4), 1.80—1.16 (8H, m, H-5—8). MS: 308 (M^+, 7), 175 (33), 136 (42), 121 (93), 91 (100).

1-(4-Hydoxyphenyl)-9-phenyl-2-nonen-1-one (**45**): Y, 77%. Yellow oil. IR: 1661. ^{1}H-NMR: 7.84 (2H, d, J=9 Hz, H-2′, 6′), 7.24—7.00 (5H, m, PhH), 6.88 (2H, d, J=9 Hz, H-3′, 5′), 7.00—6.60 (2H, m, H-2, 3), 2.60 (2H, t, J=7 Hz, H-9), 2.28 (2H, t, J=7 Hz, H-4), 1.72—1.20 (8H, m, H-5—8). MS: 308 (M^+, 27), 175 (62), 136 (71), 121 (100).

1-(4-Benzyloxyphenyl)-9-(4-methoxyphenyl)-2-nonen-1-one (**46**): Y, 82%. Pale yellow powder, mp 50—52 °C. IR: 1666. ^{1}H-NMR (500 MHz): 7.94 (2H, d, J=8.8 Hz, H-2′, 6′), 7.33—7.44 (5H, m, PhH), 7.10—6.99 (5H, m, H-3, 3′, 5′, 2″, 6″), 6.89—6.80 (3H, m, H-2, 3″, 5″), 5.13 (2H, s, PhC<u>H</u>$_2$), 3.78 (3H, s, OMe), 2.55 (2H, t, J=7.5 Hz, H-9), 2.29 (2H, q, J=7.0 Hz, H-4), 1.62—1.29 (8H, m, H-5—8). MS: 428 (M^+, 29), 211 (66), 121 (93), 91 (100).

Dehydration of 34 With *p*-TsOH: A mixture of **34** (200 mg) and *p*-TsOH (25 mg) in toluene (20 ml) was heated under reflux for 3 h. Work-up of the reaction mixture gave **48** (79 mg, 46%) as a colorless oil. IR: 1665. ^{1}H-NMR (500 MHz): 7.90 (2H, d, J=8.8 Hz, H-2′, 6′), 7.05 (1H, dt, J=15.1, 7.0 Hz, H-3), 6.89 (2H, d, J=8.8 Hz, H-3′, 5′), 6.87 (1H, br d, J=15.6 Hz, H-2), 6.79 (1H, d, J=8.5 Hz, H-5″), 6.71 (1H, dd, J=8.5, 1.7 Hz, H-6″), 6.70 (1H, br s, H-2″), 3.86, 3.85 (each 3H, s, OMe), 2.55 (2H, t, J=7.6 Hz, H-9), 2.30 (2H, m, H-4), 1.64—1.30 (8H, H-5—8). MS: 368 (M^+, 72), 151 (75), 121 (100).

With PPTS: A mixture of **34** (217 mg) and pyridinium *p*-toluenesulfonate (PPTS, 20 mg) in dry benzene (10 ml) was heated under reflux for 2 h. Work-up of the reaction mixture gave **47** (109 mg, 52%) as a colorless oil. IR: 1667. ^{1}H-NMR: 7.93 (2H, d, J=8.8 Hz, H-2′, 6′), 7.08 (2H, d, J=8.8 Hz, H-3′, 5′), 7.04 (1H, dt, J=15.2, 7.0 Hz, H-3), 6.87 (1H, dt, J=15.2, 1.0 Hz, H-2), 6.78 (1H, br d, J=8.3 Hz, H-5″), 6.71 (1H, dd, J=8.3, 1.7 Hz, H-6″), 6.70 (1H, br s, H-2″), 5.23 (2H, s, OCH_2O), 3.87, 3.85 (each 3H, s, OMe), 3.47 (3H, s, CH_2O<u>Me</u>), 2.55 (2H, t, J=7.8 Hz, H-9), 2.30 (2H, qd, J=7.0, 1.0 Hz, H-4), 1.62, 1.52 (each 2H, m, H-5, 8), 1.41—1.33 (4H, H-6, 7). MS: 412 (M^+, 100), 165 (62), 151 (75), 121 (100).

Hydrogenaton of the 2-Enes (D) to the Saturated Compounds (F) (General Procedure) The unsaturated compound(s) (D or the mixture with E) (0.1—0.5 g) in acetone (20—50 ml) was hydrogenated over 5% Pd–C (50—100 mg) for 1—4 h at a H_2 pressure of 4.5 kg/cm^2. Removal of the solvent and catalyst from the mixture, and chromatography of the product gave the saturated compound (F).

1,9-Diphenylnonan-1-one (**8**): Y, 62%. Colorless solid, mp<30 °C. IR: 1682. ^{1}H-NMR: 7.92 (2H, dd, J=8, 2 Hz, H-2′, 6′), 7.54—7.28 (3H, m, H-3′, 4′, 5′), 7.28—7.00 (5H, m, PhH), 2.94 (2H, t, J=7 Hz, H-2), 2.60 (2H, t, J=7 Hz, H-9), 1.90—1.06 (12H, H-3—8). MS: 294 (M^+, 18), 135 (25), 120 (100).

1-(4-Methoxyphenyl)-9-phenylnonan-1-one (**9**): Y, 93%. Colorless needles from ether–hexane, mp 39—40 °C. IR (KBr): 1667. ^{1}H-NMR (500 MHz): 7.94 (2H, d, J=9.0 Hz, H-2′, 6′), 7.29—7.14 (5H, m, PhH), 6.92 (2H, d, J=9.0 Hz, H-3′, 5′), 3.85 (3H, s, OMe), 2.89 (2H, t, J=7.5 Hz, H-2), 2.59 (2H, t, J=7.8 Hz, H-9), 1.76—1.56 (4H, m, H-3, 8), 1.40—1.30 (8H, m, H-4—7). MS: 324 (M^+, 21), 150 (100). *Anal*. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.21; H, 8.79.

1-(2,4-Dimethoxyphenyl)-9-phenylnonan-1-one (**10**): Y, 87%. Colorless oil. IR: 1662. ^{1}H-NMR (500 MHz): 7.77 (1H, d, J=9.0 Hz, H-6′), 7.29—7.14 (5H, m, PhH), 6.51 (1H, dd, J=9.0, 2.3 Hz, H-5′), 6.45 (1H, d, J=2.3 Hz, H-3′), 3.86, 3.84 (each 3H, s, OMe), 2.91 (2H, t, J=7.7 Hz, H-2), 2.59 (2H, t, J=8.0 Hz, H-9), 1.68—1.56 (4H, m, H-3, 8), 1.38—1.28 (8H, m, H-4—7). MS: 354 (M^+, 27), 193 (26), 180 (96), 166 (24), 165 (100).

1-(2,5-Dimethoxyphenyl)-9-phenylnonan-1-one (**11**): Y, 96%. Colorless oil. IR: 1672. ^{1}H-NMR (500 MHz): 7.21 (1H, d, J=3.5 Hz, H-6′), 7.29—7.14 (5H, m, PhH), 7.00 (1H, dd, J=9.0, 3.5 Hz, H-4′), 6.89 (1H, d, J=9.0 Hz, H-3′), 3.84, 3.78 (each 3H, s, OMe), 2.95 (2H, t, J=7.5 Hz, H-2), 2.59 (2H, t, J=8.0 Hz, H-9), 1.70—1.56 (4H, m, H-3, 8), 1.38—1.28 (8H, m, H-4—7). MS: 354 (M^+, 31), 180 (42), 165 (100).

1-(3,4-Dimethoxyphenyl)-9-phenylnonan-1-one (**12**): Y, 80%. Colorless prisms from benzene–MeOH, mp 64—65 °C. IR: 1670. ^{1}H-NMR: 7.48 (1H, s, H-2′), 7.52 (1H, dd, J=8, 2 Hz, H-6′), 7.32—7.00 (5H, m, PhH), 6.82 (1H, d, J=8 Hz, H-5′), 3.90 (2×3H, s, OMe), 2.88 (2H, t, J=7 Hz, H-2), 2.56 (2H, t, J=7 Hz, H-9), 1.88—1.16 (12H, m, H-3—8). MS: 354 (M^+, 20), 180 (100), 165 (83).

1-(2-Hydoxyphenyl)-9-phenylnonan-1-one (**14**): Y, 91%. Colorless prisms from benzene–methanol, mp 47—48 °C. IR: 1639. ^{1}H-NMR: 7.80—6.76 (9H, m, 4×ArH, PhH), 2.98 (2H, t, J=7 Hz, H-2), 2.60 (2H, t, J=7 Hz, H-9), 1.92—1.12 (12H, m, H-3, 4, 5, 6, 7, 8). MS: 310 (M^+, 12), 292 (21), 149 (35), 136 (82), 121 (100).

1-(3-Hydoxyphenyl)-9-phenylnonan-1-one (**15**): Y, 83%. Colorless needles from hexane–benzene, mp 79—81 °C. IR: 1681. ^{1}H-NMR: 7.56—6.94 (9H, m, ArH, PhH), 6.22 (1H, br s, OH), 2.92 (2H, t, J=7 Hz, H-2), 2.56 (2H, t, J=7.5 Hz, H-9), 1.80—1.12 (12H, m, H-3—8). MS: 310 (M^+, 10), 149 (22), 136 (100).

1-(4-Hydoxyphenyl)-9-phenylnonan-1-one (**16**): Y, 82%. Colorless solid, mp 45—47 °C. IR: 3285, 1663. ^{1}H-NMR (500 MHz): 7.90 (2H, d, J=8.6 Hz, H-2′, 6′), 7.28—7.13 (5H, m, PhH), 7.70 (1H, br s, OH), 6.93 (2H, d, J=8.6 Hz, H-3′, 5′), 2.91 (2H, t, J=7.6 Hz, H-2), 2.58 (2H, t, J=7.8 Hz, H-9), 1.71 (2H, quintet, J=7.8 Hz, H-8), 1.62—1.53 (2H, m, H-3), 1.38—1.25 (8H, m,

H-4—7). MS: 310 (M^+, 18), 149 (20), 136 (100).

Demethylation of 9 *p*-Methoxy derivative **9** (200 mg) in CH_2Cl_2 (10 ml) was stirred with BBr_3 (0.584 ml, 10 mol eq) for 18 h at room temperature. The mixture was poured into ice-water and extracted with $CHCl_3$, which was washed with saturated $NaHCO_3$, and concentrated. Chromatography of the product gave **16** (10 mg, 5%) from the hexane–EtOAc (4 : 1) eluate.

Demethylation of 10 The 2,4-dimethoxy derivative **10** (200 mg) in CH_2Cl_2 (10 ml) was treated with BBr_3 (0.292 ml, 5 mol eq) for 20 min at room temperature. Work-up of the product as described above gave the 2-demethylated derivative **13** (163 mg, 85%). Further demethylation of **13** (133 mg) with BBr_3 (0.584 ml, 10 mol eq) for 22 h at room temperature gave **17** (65 mg, 60%).

1-(2-Hydroxy-4-methoxyphenyl)-9-phenylnonan-1-one (**13**): Colorless solid, mp <30 °C . IR: 1630. ^{1}H-NMR (500 MHz): 12.9 (1H, s, OH), 7.65 (1H, m, H-6′), 7.29—7.15 (5H, m, PhH), 6.44—6.41 (2H, m, H-3′, 5′), 3.83 (3H, s, OMe), 2.88 (2H, t, *J*=7.6 Hz, H-2), 2.60 (2H, t, *J*=7.8 Hz, H-9), 1.72 (2H, quintet, *J*=7.8 Hz, H-8), 1.64—1.57 (2H, m, H-3), 1.40—1.30 (8H, m, H-4—7). MS: 340 (M^+, 22), 166 (67), 151 (100).

1-(2,4-Dihydroxyphenyl)-9-phenylnonan-1-one (**17**): Colorless needles from ether–hexane, mp 49—50 °C. IR (KBr): 1635. ^{1}H-NMR: 12.9 (1H, s, OH), 7.64 (1H, d, *J*=8.8 Hz, H-6′), 7.30—7.14 (5H, m, PhH), 6.42—6.36 (2H, m, H-3′, 5′), 2.87 (2H, t, *J*=7.3 Hz, H-2), 2.59 (2H, t, *J*=7.8 Hz, H-9), 1.70 (2H, quintet, *J*=7.8 Hz, H-8), 1.64—1.56 (2H, m, H-3), 1.40—1.28 (8H, m, H-4—7). MS: 326 (M^+, 27), 165 (27), 152 (87), 137 (100).

Demethylation of 11 Demethylation of the 2,5-dimethoxy derivative **11** (200 mg) with BBr_3 (5 mol eq) in CH_2Cl_2 (10 ml) for 10 min at 0 °C gave 1-(2,5-dihydroxyphenyl)-9-phenylnonan-1-one (**18**) (180 mg, 98%) as pale yellow needles from ether–hexane, mp 76—77 °C. IR (KBr): 1635. ^{1}H-NMR: 12.0 (1H, s, 2′-OH), 7.20 (1H, d, *J*=2.9 Hz, H-6′), 7.30—7.15 (5H, m, PhH), 7.00 (1H, dd, *J*=8.8, 2.9 Hz, H-4′), 6.87 (1H, d, *J*=8.8 Hz, H-3′), 5.16 (1H, br s, 5′-OH), 2.90 (2H, t, *J*=7.6 Hz, H-2), 2.59 (2H, t, *J*=7.6 Hz, H-9), 1.71 (2H, quintet, *J*=7.6 Hz, H-8), 1.63—1.57 (2H, m, H-3), 1.40—1.25 (8H, m, H-4—7). MS: 326 (M^+, 79), 308 (40), 189 (24), 165 (48), 152 (53), 137 (100). *Anal*. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.08; H, 8.06.

Hydrogenation of 46 The unsaturated ketone **46** (125 mg) in acetone (20 ml) was hydrogenated over 10% Pd–C (30 mg) at a H_2 pressure of 4 kg/cm^2 for 1 h. Removal of the solvent and catalyst and chromatography of the residue in hexane–EtOAc (3 : 1) gave three products **20** (80 mg, 65%), **49** (13 mg, 10%), and **21** (11 mg, 11%) in this order of elution.

1-(4-Benzyloxyphenyl)-9-(4-methoxyphenyl)-nonan-1-one (**20**): Colorless needles from EtOAc–hexane, mp 55—58 °C. IR: 1673. ^{1}H-NMR (500 MHz): 7.94 (2H, d, *J*=8.8 Hz, H-2′, 6′), 7.44—7.32 (5H, m, PhH), 7.08 (2H, d, *J*=8.8 Hz, H-3′, 5′), 7.00 (2H, d, *J*=8.8 Hz, H-2″, 6″), 6.82 (2H, d, *J*=8.8 Hz, H-3″, 5″), 5.13 (2H, s, H-10), 3.78 (3H, s, OMe), 2.89 (2H, t, *J*=7.8 Hz, H-2), 2.53 (2H, t, *J*=7.8 Hz, H-9), 1.74—1.55 (4H, m, H-3, 8), 1.38—1.24 (8H, m, H-4—7). MS: 430 (M^+, 25), 226 (32), 211 (27), 121 (91), 92 (20), 91 (100).

1-(4-Benzyloxyphenyl)-9-(4-methoxyphenyl)-nonan-1-ol (**49**): Pale yellow oil. IR: no CO. ^{1}H-NMR (500 MHz): 7.44—7.25 (7H, m, H-2′, 6′, PhH), 7.07 (2H, d, *J*=8.8 Hz, H-3′, 5′), 6.95 (2H, d, *J*=8.3 Hz, H-2″, 6″), 6.80 (2H, d, *J*=8.3 Hz, H-3″, 5″), 5.06 (2H, s, $PhCH_2$), 4.60 (1H, t, *J*=6.8 Hz, H-1), 3.78 (3H, s, OMe), 2.52 (2H, t, *J*=7.8 Hz, H-9), 1.27—1.78 (14H, m, H-2—8). MS: 432 (M^+, 8), 213 (80), 123 (23), 121 (81), 91 (100).

1-(4-Hydroxyphenyl)-9-(4-methoxyphenyl)-nonan-1-one (**21**): Colorless powder, mp 51—53 °C. IR: 1672. ^{1}H-NMR (500 MHz): 7.90 (2H, d, *J*=8.7 Hz, H-2′, 6′), 7.08 (2H, d, *J*=8.7 Hz, H-3′, 5′), 6.88 (2H, d, *J*=8.3 Hz, H-2″, 6″), 6.82 (2H, d, *J*=8.7 Hz, H-3″, 5″), 3.78 (3H, s, OMe), 2.89 (2H, t, *J*=7.5 Hz, H-2), 2.53 (2H, t, *J*=7.8 Hz, H-9), 1.53—1.74 (4H, m, H-3, 8), 1.24—1.37 (8H, m, H-4—7). MS: 340 (M^+, 54), 204 (48), 121 (100).

Hydrogenation of 20 Further hydrogenation of **20** (67 mg) in acetone over 10% Pd–C (20 mg) at a H_2 pressure of 4 kg/cm^2 for 2 h gave **21** (10 mg, 19%) and **49** (10 mg, 15%), with recovery of **20** (28 mg, 42%).

Hydrogenation of 47 Hydrogenation of **47** (109 mg) in acetone (10 ml) over 5% Pd–C (10 mg) at an ordinary pressure for 30 min, and chromatography (benzene : AcOEt=15 : 1) of the product gave two products, **22** (102 mg, 93%) and **50** (7 mg, 5%).

1-(4-Methoxymethoxyphenyl)-9-(3,4-dimethoxyphenyl)nonan-1-one (**22**): Colorless oil. ^{1}H-NMR (500 MHz): 7.93 (2H, d, *J*=9.3 Hz, H-2′, 6′), 7.07 (2H, d, *J*=8.8 Hz, H-3′, 5′), 6.78 (1H, d, *J*=8.8 Hz, H-5″), 6.71 (1H, dd, *J*=8.8, 1.7 Hz, H-6″), 6.70 (1H, br s, H-2″), 5.23 (2H, s, OCH_2O), 3.87, 3.85, 3.48 (each 3H, s, OMe), 3.32 (1H, br s, OH), 2.90 (2H, t, *J*=7.3 Hz, H-2), 2.54 (2H, t, *J*=7.8 Hz, H-9), 1.72, 1.58 (each 2H, m, H-3, 8), 1.40—1.30 (8H, m, H-4—7).

1-(4-Methoxymethoxyphenyl)-9-(3,4-dimethoxyphenyl)nonan-1-ol (**50**): Colorless oil. ^{1}H-NMR (500 MHz): 7.26 (2H, d, *J*=9.1 Hz, H-2′, 6′), 7.01 (2H, d, *J*=9.1 Hz, H-3′, 5′), 6.78 (1H, d, *J*=8.8 Hz, H-5″), 6.71 (1H, d, *J*=6.9 Hz, H-6″), 6.70 (1H, br s, H-2″), 5.20 (2H, s, OCH_2O), 4.62 (1H, br t, *J*=6.3 Hz, H-1), 3.90, 3.85, 3.48 (each 3H, s, OMe), 2.55 (2H, m, H-9), 1.85, 1.70, 1.60 (each 2H, m, H-2, 3, 8), 1.70—1.20 (8H, H-4—7). MS: 414 (M^+, 56), 398 (46), 167 (45), 165 (35), 151 (100).

Deprotection of 22 A mixture of **22** (97 mg) and *p*-TsOH (10 mg) in MeOH (10 ml) was heated under reflux for 3 h. Chromatography (benezene–AcOEt=4 : 1) of the product gave **23** (68.6 mg, 79%).

1-(4-Hydroxyphenyl)-9-(3,4-dimethoxyphenyl)nonan-1-one (**23**): Colorless needles from benzene–hexane, mp 100—103 °C. IR (KBr): 1671. ^{1}H-NMR: 7.90 (2H, d, *J*=8.8 Hz, H-2′, 6′), 6.87 (2H, d, *J*=8.8 Hz, H-3′, 5′), 6.79 (1H, d, *J*=8.8 Hz, H-5″), 6.71 (2H, dd, *J*=8.8, 1.7 Hz, H-6″), 6.70 (1H, br s, H-2″), 5.75 (1H, br s, OH), 3.87, 3.86 (each 3H, s, OMe), 2.89 (2H, t, *J*=7.6 Hz, H-2), 2.54 (2H, t, *J*=7.8 Hz, H-9), 1.71, 1.57 (each 2H, m, H-3, 8), 1.40—1.30 (8H, H-4—7). MS: 370 (M^+, 100), 152 (22), 151 (100).

Hydrogenation of 48 Hydrogenation of **48** (79 mg) in acetone (10 ml) over 10% Pd–C (30 mg) at an ordinary pressure for 2 h, and chromatography (benzene–AcOEt=9 : 1—4 : 1) of the product gave **23** (24 mg, 30%), **51** (26 mg, 33%), and **52** (12 mg, 16%).

1-(4-Hydroxyphenyl)-9-(3,4-dimethoxyphenyl)nonan-1-ol (**51**): Pale yellow oil. IR: no CO. ^{1}H-NMR (500 MHz): 7.21 (2H, d, *J*=8.3 Hz, H-2′, 6′), 6.80 (2H, d, *J*=8.8 Hz, H-3′, 5′), 6.79 (1H, d, *J*=7.3 Hz, H-5″), 6.71 (1H, br d, *J*=6.8 Hz, H-6″), 6.70 (1H, br s, H-2″), 4.91 (1H, br s, OH), 4.59 (1H, t, *J*=6.3 Hz, H-1), 3.87, 3.85 (each 3H, s, OMe), 2.53 (2H, t, *J*=7.8 Hz, H-9), 1.63—1.52 (4H, H-2, 8), 1.33 (10H, H-3—7). MS: 372 (M^+, 9), 354 (100).

1-(4-Hydroxyphenyl)-9-(3,4-dimethoxyphenyl)nonane (**52**): Colorless powder, mp 86—90 °C. IR: no CO. ^{1}H-NMR (500 MHz): 7.03 (2H, d, *J*=8.3 Hz, H-2′, 6′), 6.79 (1H, d, *J*=8.8 Hz, H-5′), 6.74 (2H, d, *J*=8.3 Hz, H-3′, 5′), 6.71 (1H, br d, *J*=8.8 Hz, H-6″), 6.70 (1H, br s, H-2″), 4.75 (1H, br s, OH), 3.87, 3.85 (each 3H, s, OMe), 2.55—2.50 (4H, H-1, 9), 1.56 (4H, H-2, 8), 1.35—1.29 (10H, m, H-3—7) . MS: 356 (M^+, 100).

1-(6-Benzyloxy-2-hydroxyphenyl)-3-hydroxy-11-phenylundecan-1-one (54) 2-Benzyloxy-6-hydroxyacetophenone (**53**) (908 mg, 3.8 mmol) in THF (10 ml) was added dropwise to a solution of LDA (3.0 eq) in THF–hexane (15 ml, 8 : 7) at −78 °C under an argon atmosphere and the mixture was stirred for 30 min. A solution of 9-phenylnonanal (743 mg, 3.4 mmol) and HMPA (1.3 ml) in THF (10 ml) was added dropwise to the above mixture. The whole was stirred at −78 °C for 30 min and at 0 °C for 30 min. The mixture was acidified with 1 N HCl with cooling, then extracted with AcOEt. Work-up of the extract gave, on chromatography (hexane–$CHCl_3$=1 : 9), the aldol product **54** (1.1 g, 70%) as yellow needles from Et_2O–hexane, mp 66—67 °C. IR (KBr): 1611. ^{1}H-NMR (500 MHz): 13.1 (1H, s, 2′-OH), 7.44—7.15 (11H, m, H-4′, 2×PhH), 6.60 (1H, dd, *J*=8.3, 1.2 Hz, H-3′), 6.48 (1H, d, *J*=8.3 Hz, H-5′), 5.10, 5.07 (each 1H, ABq, *J*=10.8 Hz, $PhC\underline{H}_2O$), 4.06 (1H, br s, H-3), 3.18 (1H, dd, *J*=18.5, 2.0 Hz, H-2), 2.99 (1H, dd, *J*=18.5, 9.5 Hz, H-2), 2.89 (1H, d, *J*=3.4 Hz, 3-OH), 2.60 (2H, t, *J*=7.8 Hz, H-11), 1.61 (2H, quintet, *J*=7.6 Hz, H-10), 1.38—1.06 (12H, m, H-4—9). MS: 460 (M^+, 1), 104 (36), 92 (55), 91 (100). *Anal*. Calcd for $C_{30}H_{36}O_4$: C, 78.23; H, 7.88. Found:C, 78.45; H, 7.98.

Dehydration of the Aldol 54 The aldol **54** (908 mg, 2.16 mmol) and *p*-TsOH (82 mg, 0.432 mmol) in benzene (30 ml) were heated under reflux for 30 min. The mixture was cooled, washed with saturated aqueous $NaHCO_3$, and concentrated. Chromatography (hexane–AcOEt=9 : 1) of the residue gave the enone **55** (799 mg, 84%), along with a small amount of the chromanone derivative **56**.

The Enone (**55**): Yellow solid. IR: 1639. ^{1}H-NMR (500 MHz): 13.1 (1H, s, 2′-OH), 7.44—7.15 (12H, m, H-2, 4′, 2×PhH), 7.01 (1H, td, *J*=15.1, 6.8 Hz, H-3), 6.61 (1H, d, *J*=8.0 Hz, H-5′), 6.47 (1H, d, *J*=8.0 Hz, H-3′), 5.10 (2H, s, $PhC\underline{H}_2O$), 2.60 (2H, t, *J*=7.6 Hz, H-11), 2.06 (2H, q, *J*=6.8 Hz, H-4), 1.61 (2H, t, quintet, *J*=7.6 Hz, H-10), 1.35—1.18 (10H, m, H-5—9). MS: 442 (M^+, 13), 254 (18), 253 (100), 227 (38), 163 (37), 162 (15), 137 (20), 92 (18), 91 (96).

The Chromanone (**56**): Yellow solid. IR: 1645. ^{1}H-NMR (500 MHz): 11.7 (1H, s, 2′-OH), 7.40—7.12 (6H, m, H-4′, PhH), 6.47 (1H, d, *J*=8.3 Hz, H-5′), 6.42 (1H, d, *J*=8.3 Hz, H-3′), 4.41—4.35 (1H, m, H-3), 2.78—2.56 (4H, m, H-2, 11), 1.67—1.10 (14H, m, H-4—10). MS: 352 (M^+, 70), 164 (11), 163 (100), 137 (72), 136 (14), 108 (16), 91 (50).

1-(2,6-Dihydroxyphenyl)-11-phenylundecan-1-one (57) A solution of the enone **55** (500 mg, 1.1 mmol) in acetone (100 ml) was hydrogenated over 5% Pd–C (150 mg) for 6 h at room temperature under a H_2 pressure of 4 kg/cm^2. Removal of the catalyst and the solvent from the reaction mixture, and chromatography (benzene) of the residue gave **57** (285 mg, 84%) as yel-

low needles from Et_2O–hexane, mp 76—77 °C. IR, ^{1}H-NMR, and MS: see Table 1. ^{13}C-NMR: 208.2, 161.2, 142.9, 135.7, 128.4, 128.2, 125.5, 110.0, 108.4, 44.8, 35.9, 31.5, 29.5, 29.4, 29.3, 24.4. *Anal*. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.79; H, 8.62.

References and Notes

1) XIX of Studies on Crude Drugs Effective on Visceral Larva Migrans. Part XVIII: Kiuchi F., Nakamura N., Saitoh M., Komagome K., Hiramatsu H., Takimoto N., Akao N., Kondo K., Tsuda Y., *Chem. Pharm. Bull*., **45**, 685—696 (1997).
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3) *a*) Purushothaman K. K., Sarada A., Connolly J. D., *J. Chem. Soc., Perkin Trans. 1*, **1977**, 587—588; *b*) Cooray N. F., Jansz E. R., Wimalasena S., Wijesekera T. P., Nair B. M., *Phytochemistry*, **26**, 3669—3371 (1987); *c*) Kumar N. S., Herath H. M. T. B., Karnarate V., *ibid*., **27**, 465—468 (1988); *d*) Pinto M. M. M., Kijjioa A., Tantisewie B., Yoshida M., Gottlieb O. R., *ibid*., **27**, 3988—3989 (1988).
4) Tsuda Y., Hosoi S., Goto Y., *Chem. Pharm. Bull*., **39**, 18—22 (1991).
5) Nakamura N., Kiuchi F., Tsuda Y., Kondo K., *Chem. Pharm. Bull*., **36**, 2685—2688 (1988).
6) Lopes L. M. X., Yoshida M., Gottlieb O. R., *Phytochemistry*, **21**, 751—755 (1982).
7) Nematocidal activity against second-stage larva of *Toxocara canis* was determined as described previously [Kiuchi F., Miyashita N., Tsuda Y., Kondo K., Yoshimura H., *Chem. Pharm. Bull*., **35**, 2880—2886 (1987)]. MLC was defined as the lowest concentration which gave a relative mobility (RM) after 24 h of incubation.
8) See Part XVIII.
9) Kiuchi F., Goto Y., Sugimoto N., Akao N., Kondo K., Tsuda Y., *Chem. Pharm.Bull*., **41**, 1640—1643 (1993).
10) For the synthesis of arylheptanals and arylnonanals, see Part XVIII.
11) Dean F. M., Goodchild J., Houghton L. E., Martin J. A., Morton R. B., Parton B., Price A. W., Somvichien N., *Tetrahedron Lett*., **1966**, 4153—4159.