Synthesis and Nematocidal Activity of Hydroxystilbenes[1)]

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Various (*E*)-hydroxystilbenes were synthesized from (*E*)/(*Z*) mixtures of methoxystilbenes through a new (*Z*)-(*E*) isomerization method followed by demethylation. The nematocidal activity appears when methoxystilbenes are demethylated to hydroxystilbenes. For this activity, a hydroxy group at the C-2 or C-3 position is necessary. Thus, 2-hydroxy-, 3-hydroxy-, 2,6-dihydroxy-, 3,4-dihydroxy-, 3,5-dihydroxy-, 2,2′-dihydroxy-, 3,3′-dihydroxy-, 3,4′-dihydroxy-, 2-hydroxy-4-methoxy-, 5-hydroxy-2-methoxy-, 2-hydroxy-6-methoxy-, 6-allyloxy-2-hydroxy-, 3-hydroxy-5-methoxy-, and 5-allyloxy-3-hydroxystilbenes showed rather potent nematocidal activity. The activity of 5-allyloxy-3-hydroxystilbene was the strongest [minimal lethal concentration (MLC) = 30 μM]. The activities of the (*E*) and (*Z*) isomers were comparable. The activities were also retained, though they were weaker, in the dihydro derivatives, hydroxybibenzyls.

Keywords nematocidal activity; *Toxocara canis*; structure–activity relationship; pinosylvin; methoxystilbene; (*Z*)-(*E*) isomerization; demethylation; hydroxystilbene; hydroxybibenzyl; 5-allyloxy-3-hydroxystilbene

In the course of our screening program[2a)] of crude drugs and plant materials for the activity against the second-stage larva of dog roundworm, *Toxocara canis*, we found that pinosylvin and its monomethyl ether, which were isolated from the Bangladeshi traditional medicine "devdaru" (lignum of *Cedrus deodara* LOUD),[2b)] showed strong nematocidal activity: the minimal lethal concentrations (MLC) are 0.24 and 0.16 mM, respectively. Since they are hydroxy derivatives of (*E*)-stilbene, and since some hydroxystilbenes are known to have remarkable physiological activities,[3)] we were interested in the nematocidal activity of hydroxystilbenes. This paper describes the synthesis and the structure–activity relationship of various hydroxystilbenes and related compounds.

Results and Discussion

Synthesis of (*E*)-Stilbenes and Related Compounds We planned to synthesize hydroxystilbenes by demethylation of the corresponding methoxystilbenes, which were prepared as follows.

Symmetrical (*E*)-methoxystilbenes (**1**—**3**) were obtained in satisfactory yields by reductive coupling of methoxybenzaldehydes (A) with Zn and $TiCl_4$ (Chart 1).[4)] This reaction is known to give (*E*)-stilbenes exclusively.[4)]

Unsymmetrical methoxystilbenes were synthesized by Wittig reaction of methoxybenzaldehydes (A) with benzyl or methoxybenzyltriphenylphosphonium bromide[5)] (B) in the presence of potassium *tert*-butoxide (Table I). The Wittig products (C) were a mixture of (*E*) and (*Z*) isomers, usually with predominance of the latter, and the pure (*Z*)-isomers can be isolated, in some cases, from this mixture by repeated chromatography (*e.g.*, **51**).

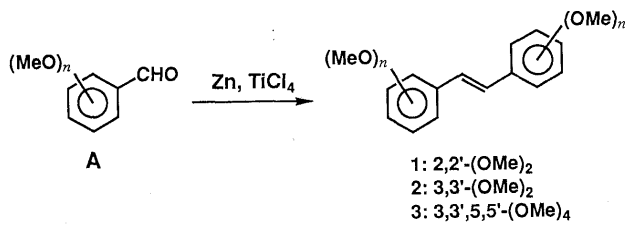


Chart 1

The (*E*)/(*Z*) mixture was isomerized to the pure (*E*)-isomer (**4**—**18**) by heating with a catalytic amount of diphenyl disulfide in tetrahydrofuran (THF).[6)] (*E*)- and (*Z*)-stilbenes are readily distinguishable by chromatography: (*Z*)-stilbenes exhibit smaller retention times in gas chromatography (GC) and greater mobilities in thin layer chromatography (TLC) than the corresponding (*E*)-isomers. The structures were determined from the proton nuclear magnetic resonance (^{1}H-NMR) spectra: the coupling constants of the olefinic protons are 16—17 Hz for (*E*)-isomers and 12 Hz for (*Z*)-isomers.

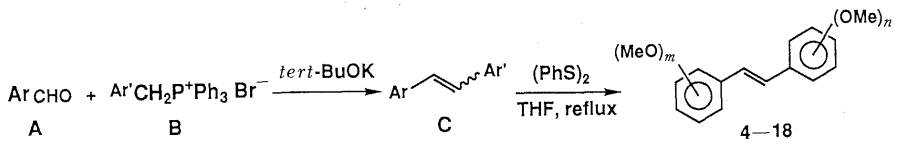
The symmetrical and unsymmetrical (*E*)-methoxystilbenes (**1**—**18**) were then demethylated with BBr_3 to the corresponding (*E*)-hydroxystilbenes (**19**—**34**) (Table II) except for the 2,4- (**8**) and 2,6-dimethoxy- (**10**), 2,4,6-trimethoxy- (**16**), and 2,3′,4,5′-tetramethoxy (**18**) derivatives, which gave complex mixtures on reaction with BBr_3. (*E*)-3,5-Dimethoxystilbene (**12**) gave, on demethylation, the fully demethylated product (**26**) and the monomethoxy derivative (**27**), which were identical with pinosylvin and pinosylvin monomethyl ether, respectively. (*E*)-2,5-Dimethoxystilbene (**9**) gave 2,5-dihydroxystilbene (**23**) and 5-hydroxy-2-methoxystilbene (**24**). The position of the methoxy group in **24** was proved by a nuclear Overhauser effect (NOE) experiment: on irradiation of the OMe group, there was a 4% enhancement for H-3 at δ 7.73 (d), and no enhancement was observed for H-6 at δ 7.03 (d) or H-4 at δ 6.68 (dd).

The hydroxystilbenes which were not available by BBr_3 demethylation of the corresponding methoxystilbenes were synthesized by direct Wittig reaction of benzylidenetriphenylphosphorane with the corresponding hydroxybenzaldehydes (Chart 2). 2,4-Dihydroxy- (**35**), 2-hydroxy-4-methoxy- (**36**), 2-hydroxy-6-methoxy- (**37**), and 6-allyloxy-2-hydroxystilbene (**38**) were prepared in this way.

2,6-Dihydroxystilbene (**41**), which was not preparable by the above two methods, was obtained by Wittig reaction of the monosilylated 2,6-dihydroxybenzaldehyde (**39**) followed by desilylation of monosilylated (*E*)-2,6-dihydroxystilbene (**40**) with tetra-*n*-butylammonium fluoride (TBAF).

The Wittig reactions of those hydroxybenzaldehydes al-

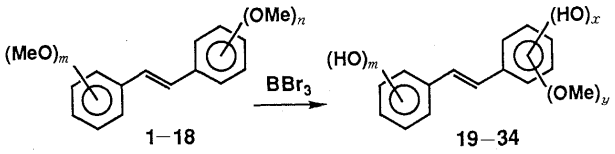
TABLE I. Synthesis of Unsymmetrical Methoxystilbenes (*E*/*Z* Mixture) by Wittig Reaction and Isomerization of the Mixture to the *E*-Isomer with Diphenyl Disulfide



			Wittig reaction			Isomerization		
A Ar	B Ar'	Stilbene C	Yield (%)	(*E*)/(*Z*) ratio	Time (h)	*E*-Isomer (Isolated yield, %)	mp (°C)	M^+ (100%)
2-$MeOC_6H_4$	Ph	2-Methoxy	95	5/95	9[a]	**4** (81)	55—56[c]	210
3-$MeOC_6H_4$	Ph	3-Methoxy	98	25/75	4[b]	**5** (87)	32—33[d]	210
4-$MeOC_6H_4$	Ph	4-Methoxy	83	35/65	6[a]	**6** (91)	134—134.5[e]	210
2,3-$(MeO)_2C_6H_3$	Ph	2,3-Dimethoxy	99	10/90	18[b]	**7** (96)	36—37	240
2,4-$(MeO)_2C_6H_3$	Ph	2,4-Dimethoxy	97	22/78	8[b]	**8** (96)	66—67	240
2,5-$(MeO)_2C_6H_3$	Ph	2,5-Dimethoxy	99	12/88	22[b]	**9** (92)	46[f]	240
2,6-$(MeO)_2C_6H_3$	Ph	2,6-Dimethoxy	97	100/ 0	—	**10**	54—55	240
3,4-$(MeO)_2C_6H_3$	Ph	3,4-Dimethoxy	97	35/65	5[a]	**11** (83)	110—110.5[g]	240
3,5-$(MeO)_2C_6H_3$	Ph	3,5-Dimethoxy	96	40/60	4[b]	**12** (96)	55[h]	240
2-MeO	4-$MeOC_6H_4$	2,4'-Dimethoxy	99	8/92	4[a]	**13** (99)	92[i]	240
3-MeO	3-$MeOC_6H_4$	3,4'-Dimethoxy	99	25/75	2[a]	**14** (95)	108—109[j]	240
4-MeO	4-$MeOC_6H_4$	4,4'-Dimethoxy	99	35/65	2[a]	**15** (98)	221—222[k]	240
2,4,6-$(MeO)_3C_6H_2$	Ph	2,4,6-Trimethoxy	99	100/ 0	—	**16**	58—59[l]	270
3,5-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	3,4',5-Trimethoxy	77	48/52[m]	1[b]	**17** (98)	55—56[n]	270
3,5-$(MeO)_2C_6H_3$	2,4-$(MeO)_2C_6H_3$	2,3',4,5'-Tetramethoxy	99	25/75	6[b]	**18** (94)	81—82[o]	300

a) 0.1 mol eq of $(PhS)_2$. *b*) 0.2 mol eq of $(PhS)_2$. *c*) Lit. mp 70 °C (Beilstein, H **6**, 693). *d*) Lit. mp 32—33 °C (J. I. G. Cadogan, E. G. Duell, and P. W. Inward, *J. Chem. Soc.*, **1962**, 4164). *e*) Lit. mp 135—135.4 °C (the same as *d*). *f*) Lit. mp 51 °C (C. T. Bahner, D. H. Brotherton, H. Kinder, W. Rich, S. L. Waton, and J. Zirkle, *J. Med. Chem.*, **12**, 722 (1969)). *g*) Lit. mp 109 °C (the same as *d*). *h*) Lit. mp 57 °C (H. Albrecht and E. H. Sheers, *J. Am. Chem. Soc.*, **76**, 603 (1954)). *i*) Lit. mp 93 °C (Beilstein, E I, **6**, 498). *j*) Lit. mp 109—110 °C [U. V. Solmssen, *J. Am. Chem. Soc.*, **65**, 2370 (1943) (*Chem. Abstr.*, **38**, 736 (9) (1944))]. *k*) Lit. mp 215 °C [B. Bottcher and F. Bauer, *Justus Liebigs Ann. Chem.*, **574**, 218 (1951) (*Chem. Abstr.*, **47**, 3856*a* (1953))]. *l*) Lit. mp 83—84 °C [D. Malho and J. Coillard, *Bull. Soc. Chim. Fr.*, **1956**, 78 (*Chem. Abstr.*, **50**, 15483*b* (1956))]. *m*) 100% (*Z*)-Isomer was used for isomerization. *n*) Lit. mp 57 °C [C. B. Cotterill, D. H. Godson, L. Jurd and T. J. King, *J. Chem. Soc.*, **1953**, 3693 [*Chem. Abstr.*, **49**, 6942*b* (1955))]. *o*) Lit. mp 57 °C (R. A. Barnes and N. N. Gerber, *J. Am. Chem. Soc.*, **77**, 3259 (1955)).

TABLE II. Demethylation of (*E*)-Methoxystilbenes with Boron Tribromide



	Methoxystilbene	BBr_3 mol eq	Product hydroxystilbene	Yield (%)	mp (°C)	M^+ (100%)
4	2-Methoxy	5	2-Hydroxy	**19** (68)	149—150[a]	196
5	3-Methoxy	6	3-Hydroxy	**20** (95)	128—129[b]	196
6	4-Methoxy	3	4-Hydroxy	**21** (53)	195—196[c]	196
7	2,3-Dimethoxy	10	2,3-Dihydroxy	**22** (82)	118—119	212
9	2,5-Dimethoxy	5	2,5-Dihydroxy	**23** (39)	166—169	212
			5-Hydroxy-2-methoxy	**24** (12)	121—124	226
11	3,4-Dimethoxy	6	3,4-Dihydroxy	**25** (94)	132—134[d]	212
12	3,5-Dimethoxy	3	3,5-Dihydroxy	**26** (51)	157—158[e]	212
			3-Hydroxy-5-methoxy	**27** (43)	121—124[f]	226
1	2,2'-Dimethoxy	10	2,2'-Dihydroxy	**28** (66)	197—198[g]	212
13	2,4'-Dimethoxy	10	2,4'-Dihydroxy	**29** (19)	192—194	212
2	3,3'-Dimethoxy	7	3,3'-Dihydroxy	**30** (79)	152—153	212
14	3,4'-Dimethoxy	7	3,4'-Dihydroxy	**31** (57)	216—218	212
15	4,4'-Dimethoxy	7	4,4'-Dihydroxy	**32** (96)	288—289[h]	212
17	3,4',5-Trimethoxy	7	3,4',5-Trihydroxy	**33** (99)	256—257[i]	228
3	3,3',5,5'-Tetramethoxy	7	3,3',5,5'-Tetrahydroxy	**34** (87)	>300[j]	244

a) Lit. mp 146—147 °C [D. F. D. Tar and Y. W. Chu, *J. Am. Chem. Soc.*, **76**, 1986, (1954) (*Chem. Abstr.*, **49**, 6191*g* (1955))]. *b*) Lit. mp 178 °C [K. Friedrick and H. G. Henning, *Chem. Ber.*, **92**, 2944 (1959) (*Chem. Abstr.*, **54**, 5561*c* (1960))]. *c*) Lit. mp 186 °C (the same as *b*). *d*) Lit. mp 168—170 °C (J. E. Sinsheimer and R. V. Smith, *Biochem. J.*, **111**, 35 (1969)). *e*) Lit. mp 153—155 °C [C. Alverez-Novoa, H. Erdtman, and G. Lindstedt, *Acta Chem. Scand.*, **4**, 444 (1950) (*Chem. Abstr.*, **45**, 2482*e* (1951))]. *f*) Lit. mp 118—119 °C (the same as *e*). *g*) Lit. mp 197 °C [N. P. Buu-Hoi and G. Saint-Ruf, *Bull. Soc. Chim. Fr.*, **3**, 955 (1967) (*Chem. Abstr.*, **67**, 53787*b* (1967))]. *h*) Lit. mp 285—286 °C [Fr. Pat. 1534311 (*Chem. Abstr.*, **72**, 3215*w*, (1970))]. *i*) Lit. mp 256—257 °C (S. Nonomura, H. Kanagawa, and A. Makimoto, *Yakugaku Zasshi*, **83**, 988 (1963)). *j*) Lit. mp 320 °C (E. Reimann, *Justus Liebigs Ann. Chem.*, **750**, 109 (1971)).

ways produced exclusively, the (*E*)-isomers (proved by the coupling constants of the olefinic protons, $J = 17$ Hz, in the ^{1}H-NMR spectra), though the yields were not satisfactory.

(*E*)-5-Alkoxy-3-hydroxystilbenes with an ethyl to tetradecyl group (**42—50**) were prepared by alkylation of (*E*)-3,5-dihydroxystilbene (**26**) with the corresponding alkyl

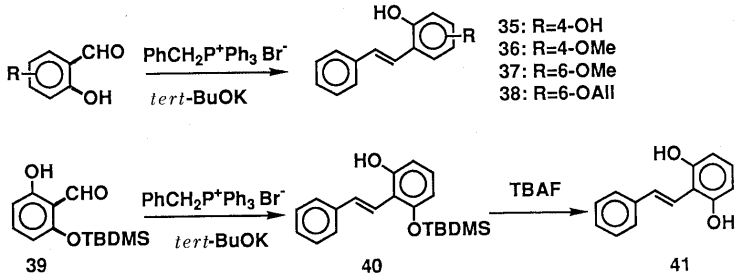
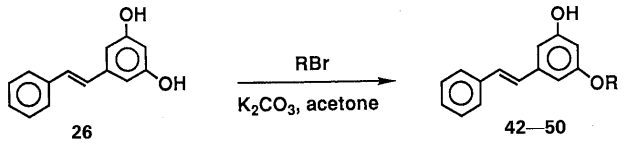


Chart 2

TABLE III. Synthesis and Characterization of 5-Alkoxy-3-hydroxystilbenes



R	Product stilbene	Yield (%)	mp (°C)	^{1}H-NMR (δ)		MS M^+ (%)	Formula	Analysis (%) Calcd		Found	
				Me	$-OCH_2-$			C	H	C	H
C_2H_5	3-Hydroxy-5-ethoxy	**42** (20)	89.5—90.5	1.41	4.04	240 (100)	$C_{16}H_{16}O_2$	79.79	6.71	79.96	6.77
C_3H_7	3-Hydroxy-5-propoxy	**43** (34)	67—68	1.20	3.92	254 (99)	$C_{17}H_{18}O_2$	80.28	7.13	80.04	7.21
C_3H_5	3-Hydroxy-5-allyloxy	**44** (38)	59—60	—	—	252 (100)	$C_{17}H_{16}O_2$	80.92	6.39	81.12	6.39
C_4H_9	3-Hydroxy-5-butoxy	**45** (35)	64.5—65.5	0.98	3.97	268 (100)	$C_{18}H_{20}O_2$	80.56	7.51	80.85	7.58
C_5H_{11}	3-Hydroxy-5-pentyloxy	**46** (26)	51—53	0.94	3.96	282 (100)	$C_{19}H_{22}O_2$	80.81	7.85	80.85	7.93
C_6H_{13}	3-Hydroxy-5-hexyloxy	**47** (36)	52—53	0.88	3.95	296 (99)	$C_{20}H_{24}O_2$	81.04	8.16	81.19	8.26
C_7H_{15}	3-Hydroxy-5-heptyloxy	**48** (41)	56.5—57	0.90	3.96	310 (85)	$C_{21}H_{26}O_2$	81.25	8.44	81.18	8.52
C_8H_{17}	3-Hydroxy-5-octyloxy	**49** (40)	55.5—56	0.89	3.95	324 (84)	$C_{22}H_{28}O_2$	81.44	8.70	81.47	8.83
$C_{10}H_{21}$	3-Hydroxy-5-decyloxy	**50** (53)	58—60	0.88	3.96	352 (85)	$C_{24}H_{32}O_2$	81.77	9.15	81.77	9.27

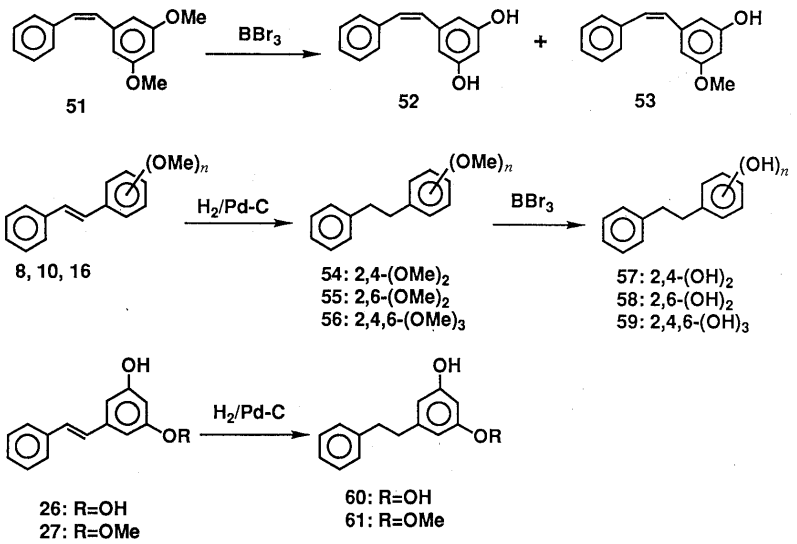


Chart 3

bromide in acetone in the presence of K_2CO_3. (*E*)-5-Allyloxy-3-hydroxystilbene (**44**) was prepared by a similar alkylation with allyl bromide (Table III).

(*Z*)-3,5-Dihydroxystilbene (**52**) and its monomethyl ether (**53**) were prepared by demethylation of (*Z*)-3,5-dimethoxystilbene (**51**) with BBr_3.

Hydroxybibenzyls (**57**—**59**) were prepared by hydrogenation of the (*E*)-methoxystilbenes (**8**, **10**, and **16**) over 10% Pd–C followed by demethylation of methoxybibenzyls (**54**—**56**). The hydroxybibenzyls (**60** and **61**) were prepared by hydrogenation of hydroxystilbenes (**26** and **27**) (Chart 3).

Nematocidal Activity of (*E*)-Stilbenes and Related Compounds Nematocidal activity of the above synthesized compounds toward the second-stage larvae of *Toxocara canis* are listed in Table IV. (*E*)-Stilbene and its methoxy derivatives (**1**—**18**) were inactive at a concentration of 0.1 mg/ml [relative mobility (RM) = 100 after 24 h] except for 3-methoxystilbene (**2**), which showed a weak activity (RM = 67 after 24 h).

The nematocidal activity appeared when (*E*)-methoxystilbenes were demethylated to (*E*)-hydroxystilbenes. (*E*)-2-Hydroxy- and (*E*)-3-hydroxystilbene (**19** and **20**) show-

TABLE IV. Nematocidal Activity of Stilbenes and Their Derivatives

Compound No.	Name stilbene	RM value (0.1 mg/ml) 6 h	24 h	MLC (mM)
	(*E*)-Stilbene	100	100	—
(*E*)-Methoxystilbenes				
4	2-Methoxy	100	100	—
5	3-Methoxy	100	67	—
6	4-Methoxy	100	100	—
7	2,3-Dimethoxy	100	100	—
8	2,4-Dimethoxy	100	100	—
9	2,5-Dimethoxy	100	100	—
10	2,6-Dimethoxy	100	100	—
11	3,4-Dimethoxy	100	100	—
12	3,5-Dimethoxy	100	100	—
1	2,2'Dimethoxy	100	100	—
13	2,4'-Dimethoxy	100	100	—
2	3,3'-Dimethoxy	100	100	—
14	3,4'-Dimethoxy	100	100	—
15	4,4'-Dimethoxy	100	100	—
16	2,4,6-Trimethoxy	100	100	—
17	3,4',5-Trimethoxy	100	100	—
18	2,3',4,5'-Tetramethoxy	100	100	—
3	3,3',5,5'-Tetramethoxy	100	100	—
(*E*)-Hydroxystilbenes				
19	2-Hydroxy	50	0	0.1
20	3-Hydroxy	59	0	0.1
21	4-Hydroxy	94	67	—
22	2,3-Dihydroxy	67	67	—
35	2,4-Dihydroxy	43	33	—
23	2,5-Dihydroxy	100	100	—
41	2,6-Dihydroxy	88	0	0.31
25	3,4-Dihydroxy	33	0	0.2
26	3,5-Dihydroxy	0	0	0.24
28	2,2'-Dihydroxy	33	0	0.47
29	2,4'-Dihydroxy	67	22	—
30	3,3'-Dihydroxy	33	0	0.24
31	3,4'-Dihydroxy	33	0	0.4
32	4,4'-Dihydroxy	100	100	—
33	3,4',5-Trihydroxy	100	100	—
34	3,3',5,5'-Tetrahydroxy	100	100	—
36	2-Hydroxy-4-methoxy	0	0	0.06
24	5-Hydroxy-2-methoxy	100	0	0.32
37	2-Hydroxy-6-methoxy	35	0	0.13
38	2-Hydroxy-6-allyloxy	49	0	0.06
27	3-Hydroxy-5-methoxy	0	0	0.16
42	3-Hydroxy-5-ethoxy	40	2	—
43	3-Hydroxy-5-propoxy	51	1	—
44	3-Hydroxy-5-allyloxy	38	0	0.03
45	3-Hydroxy-5-butoxy	96	2	—
46	3-Hydroxy-5-pentyloxy	100	53	—
47	3-Hydroxy-5-hexyloxy	100	77	—
48	3-Hydroxy-5-heptyloxy	100	100	—
49	3-Hydroxy-5-octyloxy	100	100	—
50	3-Hydroxy-5-decyloxy	100	100	—
(*Z*)-Stilbenes				
51	(*Z*)-3,5-Dimethoxy	100	100	—
52	(*Z*)-3,5-Dihydroxy	100	100	
53	(*Z*)-3-Hydroxy-5-methoxy	33	0	0.12
Bibenzyls				
57	2,4-Dihydroxy	43	37	—
58	2,6-Dihydroxy	100	4	—
60	3,5-Dihydroxy	100	62	—
61	3-Hydroxy-5-methoxy	33	0	0.1—0.2
59	2,4,6-Trihydroxy	100	92	—

ed very strong nematocidal activity, with MLCs of 0.1 mM, respectively, while the activity of (*E*)-4-hydroxystilbene (**21**) was very weak. When an additional hydroxy group was introduced in the same benzene ring, the activity was decreased (**22**, **23**, and **35**), but the activities of 2,6-dihydroxy- (**37**), 3,4-dihydroxy- (**25**) and 3,5-dihydroxystilbene (**26**) were strong. When one of the hydroxy groups in dihydroxystilbene was masked by methylation, the activity was regenerated or increased (**35** *vs.* **36**, **23** *vs.* **24**, **41** *vs.* **37**, and **26** *vs.* **27**). Among these compounds, 2-hydroxy-4-methoxystilbene (**36**) showed the strongest nematocidal activity, the MLC of which was 60 μM. 6-Allyloxy-2-hydroxystilbene (**38**) showed a very strong nematocidal activity, whose MLC is 60 μM, the activity being stronger than that of 2-hydroxy-6-methoxystilbene (**37**).

Stilbenes carrying two hydroxy groups on separate benzene rings are active (**28**—**31**), but the 4,4'-dihydroxy derivative (**32**) was again inactive suggesting that a hydroxy group at position C-4 decreases the activity.

When (*E*)-3,5-dihydroxystilbene (**26**) is further substituted by hydroxy groups at position C-4' or C-3',5', the resulting compounds, (*E*)-3,4',5-trihydroxystilbene (**33**) and (*E*)-3,3',5,5'-tetrahydroxystilbene (**34**), become completely inactive.

Ahad *et al.*[7] found that, for alkyl 2,4-dihydroxybenzoates, the nematocidal activity increases as the alkyl chain length increases up to octyl ester, and the activity then decreases with further increase of the alkyl chain length. Since the nematocidal activity of pinosylvin monomethyl ether (**27**) is stronger than that of pinosylvin (**26**), the activities of monomethyl to decyl ethers of (*E*)-3,5-dihydroxystilbene were then examined to see whether the activity increases with increase of the alkyl chain length or not. The result was as follows: (*E*)-3-hydroxy-5-methoxystilbene (**27**) is strongly active and the activity decreases with increase of the alkyl chain length (**42**—**50**). (*E*)-5-Allyloxy-3-hydroxystilbene (**44**) showed the strongest nematocidal activity, the MLC of which is 30 μM.

For comparison of the nematocidal activity of (*E*)- and (*Z*)-isomers, the activities of (*Z*)-3,5-dimethoxy-, (*Z*)-3,5-dihydroxy-, and (*Z*)-3-hydroxy-5-methoxystilbenes were examined. (*Z*)-3,5-Dimethoxy- (**51**) and (*Z*)-3,5-dihydroxystilbene (**52**) are inactive, while (*Z*)-3-hydroxy-5-methoxystilbene (**53**) is strongly active (MLC = 0.12 mM), the activity being comparable with that of the (*E*)-isomer (**27**) (MLC = 0.16 mM).

The nematocidal activities of hydroxybibenzyls were studied to examine whether the double bond present in stilbenes is actually necessary for the nematocidal activity or not. 2,4-Dihydroxybibenzyl (**57**) had comparable nematocidal activity (RM = 37 after 24 h) to (*E*)-2,4-dihydroxystilbene (**35**) (RM = 33). 3,5-Dihydroxybibenzyl (**60**) showed a weak activity, but its monomethyl ether (**61**) showed a very strong activity (MLC = 0.1—0.2 mM), comparable to that of (*E*)-3-hydroxy-5-methoxystilbene (**27**) (MLC = 0.16 mM), suggesting that the double bond present in the (*E*)-stilbenes is not essential for the nematocidal activity.

Conclusion

The nematocidal activity of (*E*)-stilbenes appears when they are hydroxylated and compounds without a hydroxy group showed no activity. For this activity, a hydroxy group is necessary at the C-2 or C-3 position. Introduction of an additional hydroxy group (dihydroxystilbenes) decreased the activity in terms of MLC. Tri- and tetrahydroxystilbenes were inactive. The activities of dihydroxystilbenes increase

when one of the hydroxy group is masked by a methyl or an allyl group. The activities of (*E*)- and (*Z*)-isomers are comparable and the activities are retained, though they are weaker, in the dihydro derivatives.

Experimental

Melting points were measured on a Yanagimoto micro hot stage melting point apparatus and are uncorrected. Unless otherwise noted, ^{1}H-NMR spectra were measured in $CDCl_3$ solutions with tetramethylsilane as an internal standard and the chemical shifts are given in δ values. Mass spectra (MS) and high resolution mass spectra (HRMS) were taken on a Hitachi M-80 spectrometer and M^+ and major peaks are given by m/z (%). Fuji-Davison BW-820MH (silica gel) was used for column chromatography.

Assay Method Nematocidal activity was determined according to the method previously described.[8] For one assay, 20 second-stage larvae of dog roundworm, *Toxocara canis*, were incubated with the test solution in a Corning cell well at 37 °C and the behavior of the larvae was observed under a microscope at 1, 3, 6, and 24 h. All assays were done in duplicate. The test sample was prepared by dissolving the sample in dimethyl sulfoxide (DMSO), which was then diluted appropriately with 0.75% saline to give 2% DMSO concentration in the solution and used in the assay. The nematocidal activity was evaluated in terms of the RM value[8]: a smaller RM value indicates a stronger nematocidal activity, and when all the larvae are killed, this value becomes zero. MLC was defined as the lowest concentration giving an RM value of zero after 24 h incubation.

Symmetrical (*E*)-Methoxystilbenes (General Procedure) A suspension of zinc powder (3 mol eq) in dioxane was added slowly to a mixture of a methoxybenzaldehyde and $TiCl_4$ (1.5 mol eq) in dioxane at −10 °C under an argon atmosphere. The yellow solution immediately changed to purple and then turned dark brown. After refluxing for 3—5 h, the mixture was poured into ice-water, and extracted with ether. The ethereal layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated. Purification of the residue by column chromatography gave a symmetrical methoxystilbene.

(*E*)-2,2′-Dimethoxystilbene (**1**): Yield 71%. Colorless needles from hexane–ether, mp 132—133 °C (lit. 137 °C).[9] ^{1}H-NMR (270 MHz): 3.84 (6H, s, 2×OMe), 6.84 (2H, d, J=8 Hz, H-3,3′), 6.95 (2H, t, J=8 Hz, H-4,4′), 7.24 (2H, t, J=8 Hz, H-5,5′), 7.47 (2H, s, –CH=CH–), 7.64 (2H, d, J=8 Hz, H-6,6′).

(*E*)-3,3′-Dimethoxystilbene (**2**): Yield 57%. Colorless needles from hexane–ether, mp 101—102 °C (lit. 100—101 °C).[10] ^{1}H-NMR (270 MHz): 3.85 (6H, s, 2×OMe), 6.82 (2H, dd, J=8, 2 Hz, H-4,4′), 7.04 (2H, d, J=2 Hz, H-2,2′), 7.06 (2H, s, –CH=CH–), 7.12 (2H, br d, J=8 Hz, H-6,6′), 7.28 (2H, br t, J=8 Hz, H-5,5′).

(*E*)-3,3′,5,5′-Tetramethoxystilbene (**3**): Yield 42%. Colorless needles from hexane–acetone, mp 141—142 °C. ^{1}H-NMR (400 MHz): 3.83 (12H, s, 4×OMe), 6.40 (2H, t, J=2 Hz, H-4,4′), 6.65 (4H, d, J=2 Hz, H-2,6,2′,6′), 7.00 (2H, s, –CH=CH–). *Anal.* Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.07; H, 6.74.

Unsymmetrical Methoxystilbenes (General Procedure) The arylmethylenetriphenylphosphonium bromide (1.2 mol eq) was stirred with potassium *tert*-butoxide (1.2 mol eq) in THF (50 ml) at −10 °C and methoxybenzaldehyde (500 mg) was added to the reaction mixture with stirring. After 30 min, the reaction mixture was poured into water, neutralized with 1 N HCl, and extracted with ether. The organic layer was dried over anhydrous sodium sulfate, then concentrated, and the residue was purified by column chromatography to yield an (*E*)/(*Z*) mixture of methoxystilbenes. The yield and (*E*)/(*Z*) ratio of each product are given in Table I.

Conversion of (*E*/*Z*)-Methoxystilbenes into the (*E*)-Isomers (General Procedure) The above mixture of methoxystilbene was heated under reflux in THF with diphenyl disulfide (0.1—0.2 mol eq). The solvent was removed from the reaction mixture by evaporation and the residue was purified by column chromatography to yield (*E*)-methoxystilbene. The amount of $(PhS)_2$ used in the conversion reaction, reaction time, yield of the product, melting point, and MS (M^+) are given in Table I. ^{1}H-NMR data obtained on a 400 MHz spectrometer are as follows.

(*E*)-2-Methoxystilbene (**4**): Colorless needles from hexane–ether. ^{1}H-NMR: 3.88 (3H, s, OMe), 6.88 (1H, d, J=8 Hz, H-3), 6.96 (1H, t, J=8 Hz, H-5), 7.11, 7.49 (each 1H, d, J=16 Hz, –CH=CH–), 7.18—7.39 (2H, m, H-4,4′), 7.34 (2H, t, J=8 Hz, H-3′,5′), 7.54 (2H, d, J=8 Hz, H-2′,6′), 7.60 (1H, dd, J=8, 2 Hz, H-6).

(*E*)-3-Methoxystilbene (**5**): Colorless needles from hexane. ^{1}H-NMR: 3.85 (3H, s, OMe), 6.82 (1H, ddd, J=7, 2.7, 1 Hz, H-4), 7.04 (1H, dd, J=2.7, 1 Hz, H-2), 7.06, 7.10 (each 1H, d, J=17 Hz, –CH=CH–), 7.12 (1H, dt, J=7, 2.7 Hz, H-6), 7.21 (1H, t, J=7 Hz, H-5), 7.25 (1H, td, J=7, 2 Hz, H-4′), 7.35 (2H, t, J=7 Hz, H-3′,5′), 7.50 (2H, d, J=7 Hz, H-2′,6′).

(*E*)-4-Methoxystilbene (**6**): Colorless needles from hexane–ether. ^{1}H-NMR: 3.80 (3H, s, OMe), 6.89 (2H, d, J=9 Hz, H-3,5), 6.96, 7.05 (each 1H, d, J=16.5 Hz, –CH=CH–), 7.21 (1H, tt, J=8, 2 Hz, H-4′), 7.33 (2H, td, J=8, 2 Hz, H-3′,5′), 7.44 (2H, d, J=9 Hz, H-2,6), 7.50 (2H, br d, J=8 Hz, H-2′,6′).

(*E*)-2,3-Dimethoxystilbene (**7**): Colorless plates from hexane. ^{1}H-NMR: 3.82, 3.86 (each 3H, s, OMe), 6.83 (1H, dd, J=8.2, 1.5 Hz, H-4), 7.05 (1H, br t, J=8 Hz, H-4′), 7.12, 7.45 (each 1H, d, J=17 Hz, –CH=CH–), 7.20—7.30 (2H, m, H-5,6), 7.36 (2H, t, J=8 Hz, H-3′,5′), 7.54 (2H, br d, J=8 Hz, H-2′,6′). *Anal.* Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.95; H, 6.74.

(*E*)-2,4-Dimethoxystilbene (**8**): Colorless needles from hexane. ^{1}H-NMR: 3.83, 3.87 (each 3H, s, OMe), 6.46 (1H, d, J=3 Hz, H-3), 6.51 (1H, dd, J=8.5, 3 Hz, H-5), 6.98, 7.38 (each 1H, d, J=16 Hz, –CH=CH–), 7.20 (1H, tt, J=7, 1 Hz, H-4′), 7.31 (2H, t, J=7 Hz, H-3′,5′), 7.50 (2H, br d, J=7 Hz, H-2′,6′), 7.52 (1H, d, J=8 Hz, H-6). *Anal.* Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.96; H, 6.66.

(*E*)-2,5-Dimethoxystilbene (**9**): Colorless needles from hexane. ^{1}H-NMR: 3.81, 3.84 (each 3H, s, OMe), 6.78 (1H, dd, J=9, 3 Hz, H-4), 6.82 (1H, d, J=9 Hz, H-3), 7.08, 7.44 (each 1H, d, J=16.5 Hz, –CH=CH–), 7.13 (1H, d, J=3 Hz, H-6), 7.23 (1H, tt, J=8, 1 Hz, H-4′), 7.32 (2H, t, J=8 Hz, H-3′,5′), 7.53 (2H, dd, J=8, 1 Hz, H-2′,6′).

(*E*)-2,6-Dimethoxystilbene (**10**): Colorless needles from hexane–ether. ^{1}H-NMR: 3.89 (6H, s, 2×OMe), 6.59 (2H, d, J=8.4 Hz, H-3,5), 7.14 (1H, t, J=8.4 Hz, H-4), 7.20 (1H, t, J=7.5 Hz, H-4′), 7.33 (2H, t, J=7.5 Hz, H-3′,5′), 7.43, 7.56 (each 1H, d, J=16.5 Hz, –CH=CH–), 7.52 (2H, d, J=7.5 Hz, H-2′,6′). *Anal.* Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.98; H, 6.70.

(*E*)-3,4-Dimethoxystilbene (**11**): Colorless needles from hexane–ether. ^{1}H-NMR: 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 6.84 (1H, d, J=8 Hz, H-5), 6.96, 7.05 (each 1H, d, J=16.5 Hz, –CH=CH–), 7.05 (1H, d, J=8 Hz, H-6), 7.08 (1H, s, H-2), 7.22 (1H, t, J=7 Hz, H-4′), 7.35 (2H, t, J=7 Hz, H-3′,5′), 7.48 (2H, d, J=7 Hz, H-2′,6′).

(*E*)-3,5-Dimethoxystilbene (**12**): Colorless needles from ethanol. ^{1}H-NMR: 3.83 (6H, s, 2×OMe), 6.38 (1H, t, J=2 Hz, H-4), 6.66 (2H, d, J=2 Hz, H-2,6), 7.02, 7.08 (each 1H, d, J=17 Hz, –CH=CH–), 7.25 (1H, tt, J=7, 2 Hz, H-4′), 7.36 (2H, td, J=7, 2 Hz, H-3′,5′), 7.50 (2H, dd, J=7, 2 Hz, H-2′,6′).

(*E*)-2,4′-Dimethoxystilbene (**13**): Colorless needles from hexane–ether. ^{1}H-NMR: 3.80, 3.88 (each 3H, s, OMe), 6.88 (2H, d, J=9 Hz, H-3′, 5′), 6.89 (1H, d, J=8 Hz, H-3), 6.94 (1H, t, J=8 Hz, H-5), 7.04, 7.33 (each 1H, d, J=16 Hz, –CH=CH–), 7.21 (1H, td, J=8, 2 Hz, H-4), 7.45 (2H, d, J=9 Hz, H-2′, 6′), 7.54 (1H, dd, J=8, 2 Hz, H-6).

(*E*)-3,4′-Dimethoxystilbene (**14**): Colorless needles from hexane–ether. ^{1}H-NMR: 3.82, 3.84 (each 3H, s, OMe), 6.78 (1H, dd, J=8, 2.5 Hz, H-4), 6.89 (2H, J=9 Hz, H-3′,5′), 6.94, 7.04 (each 1H, d, J=16 Hz, –CH=CH–), 7.02 (1H, d, J=2.5 Hz, H-2), 7.08 (1H, d, J=8 Hz, H-6), 7.25 (1H, t, J=8 Hz, H-5), 7.44 (2H, d, J=9 Hz, H-2′,6′).

(*E*)-4,4′-Dimethoxystilbene (**15**): Colorless leaflets from benzene–acetone. ^{1}H-NMR: 3.78 (6H, s, 2×OMe), 6.93 (4H, d, J=8.5 Hz, H-3,5,3′,5′), 7.03 (2H, s, –CH=CH–), 7.50 (4H, d, J=8.5 Hz, H-2,6,2′,6′).

(*E*)-2,4,6-Trimethoxystilbene (**16**): Colorless needles from hexane. ^{1}H-NMR: 3.57, 3.83, 3.88 (each 3H, s, OMe), 6.16 (2H, s, H-3,5), 7.17 (1H, tt, J=7.5, 1 Hz, H-4′), 7.28 (2H, t, J=7.5 Hz, H-3′,5′), 7.34, 7.43 (each 1H, d, J=16.5 Hz, –CH=CH–), 7.52 (2H, dd, J=7.5, 1 Hz, H-2′,6′).

(*E*)-3,4′,5-Trimethoxystilbene (**17**): Colorless needles from hexane–ether. ^{1}H-NMR: 3.80 (9H, s, 3×OMe), 6.34 (1H, t, J=2 Hz, H-4), 6.64 (2H, d, J=2 Hz, H-2,6), 6.88, 7.04 (each 1H, d, J=16 Hz, –CH=CH–), 6.90 (2H, d, J=8 Hz, H-3′,5′), 7.42 (2H, d, J=8 Hz, H-2′,6′).

(*E*)-2,3′,4,5′-Tetramethoxystilbene (**18**): Colorless needles from hexane–acetone. ^{1}H-NMR (270 MHz): 3.84 (12H, s, 4×OMe), 6.35 (1H, t, J=2.3 Hz, H-4′), 6.46 (1H, d, J=2 Hz, H-3), 6.52 (1H, dd, J=8, 2 Hz, H-5), 6.66 (2H, d, J=2.3 Hz, H-2′,6′), 6.92, 7.36 (each 1H, d, J=17 Hz, –CH=CH–), 7.48 (1H, d, J=8 Hz, H-6).

(*E*)-Hydroxystilbenes (General Procedure) Boron tribromide (3—10 mol eq) was added to a stirred solution of methoxystilbene (200—300 mg) in CH_2Cl_2 (20—30 ml) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 10—30 min, then poured into ice-water, and extracted with AcOEt. The AcOEt layer was washed with brine, dried, and concentrated. The residue was purified by column chromatography to give (*E*)-hydroxystilbene. The yield, melting point, and MS of the product are indicated in Table II. The ^{1}H-NMR spectra were measured

in CD_3OD solution on a 400 MHz spectrometer.

(*E*)-2-Hydroxystilbene (**19**): Colorless needles from hexane–ether. ^{1}H-NMR: 6.97 (1H, dd, J=8, 2 Hz, H-3), 6.82 (1H, t, J=8 Hz, H-4), 7.06 (1H, td, J=8, 2 Hz, H-5), 7.14, 7.48 (each 1H, d, J=17 Hz, –CH=CH–), 7.19 (1H, br t, J=8 Hz, H-4′), 7.33 (2H, t, J=8 Hz, H-3′,5′), 7.54 (2H, d, J=8 Hz, H-2′,6′), 7.57 (1H, d, J=8 Hz, H-6).

(*E*)-3-Hydroxystilbene (**20**): Colorless needles from hexane–ether. ^{1}H-NMR: 6.73 (1H, ddd, J=8, 3, 1 Hz, H-4), 6.99 (1H, dd, J=3, 1 Hz, H-2), 7.03, 7.08 (each 1H, d, J=17 Hz, –CH=CH–), 7.10 (1H, br d, J=8 Hz, H-6), 7.22 (1H, t, J=8 Hz, H-5), 7.25 (1H, tt, J=8, 2 Hz, H-4′), 7.35 (2H, t, J=8 Hz, H-3′,5′), 7.51 (2H, br d, J=8 Hz, H-2′,6′).

(*E*)-4-Hydroxystilbene (**21**): Colorless needles from hexane–acetone. ^{1}H-NMR: 6.76 (2H, d, J=8 Hz, H-3,5), 6.94, 7.06 (each 1H, d, J=18 Hz, –CH=CH–), 7.17 (1H, td, J=8, 2 Hz, H-4′), 7.29 (2H, t, J=8 Hz, H-3′,5′), 7.35 (2H, br d, J=8 Hz, H-2′,6′), 7.47 (2H, d, J=8 Hz, H-2,6).

(*E*)-2,3-Dihydroxystilbene (**22**): Colorless needles from hexane–acetone. ^{1}H-NMR: 6.62—6.73 (2H, m, H-4,5), 7.05 (1H, dd, J=8, 2 Hz, H-6), 7.13, 7.48 (each 1H, d, J=16 Hz, –CH=CH–), 7.19 (1H, t, J=8 Hz, H-4′), 7.32 (2H, t, J=8 Hz, H-3′,5′), 7.55 (2H, d, J=8 Hz, H-2′,6′). *Anal.* Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.32; H, 5.77.

(*E*)-2,5-Dihydroxystilbene (**23**): Colorless needles from hexane–ether. ^{1}H-NMR: 6.57 (1H, dd, J=9, 3 Hz, H-4), 6.68 (1H, d, J=9 Hz, H-3), 7.00 (1H, d, J=3 Hz, H-6), 7.07, 7.43 (each 1H, d, J=17 Hz, –CH=CH–), 7.21 (1H, tt, J=7, 1 Hz, H-4′), 7.32 (2H, t, J=7 Hz, H-3′,5′), 7.51 (2H, br d, J=7 Hz, H-2′,6′). *Anal.* Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.34; H, 5.80.

(*E*)-5-Hydroxy-2-methoxystilbene (**24**): Colorless needles from hexane–ether. ^{1}H-NMR ($CDCl_3$): 3.83 (3H, s, OMe), 6.68 (1H, dd, J=9, 3 Hz, H-4), 7.73 (1H, d, J=9 Hz, H-3), 7.03 (1H, d, J=3 Hz, H-6), 7.06, 7.42 (each 1H, d, J=17 Hz, –CH=CH=), 7.22 (1H, tt, J=7.5, 1 Hz, H-4′),7.33 (2H, t, J=7.5 Hz, H-3′,5′), 7.51 (2H, br d, J=7.5 Hz, H-2′,6′). HRMS m/z (M^+): Calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0989.

(*E*)-3,4-Dihydroxystilbene (**25**): Colorless needles from hexane–ether. ^{1}H-NMR: 6.74 (1H, d, J=8 Hz, H-5), 6.86 (1H, dd, J=8, 2 Hz, H-6), 6.88, 6.96 (each 1H, d, J=17 Hz, –CH=CH–), 7.02 (1H, d, J=2 Hz, H-2), 7.19 (1H, tt, J=8, 2 Hz, H-4′), 7.30 (2H, t, J=8 Hz, H-3′,5′), 7.46 (2H, dd, J=8, 2 Hz, H-2′,6′).

(*E*)-3,5-Dihydroxystilbene (Pinosylvin) (**26**): Colorless needles from hexane–ether. ^{1}H-NMR ($CDCl_3$): 3.30 (2H, s, OH), 6.20 (1H, t, J=2 Hz, H-4), 6.50 (2H, d, J=2 Hz, H-2,6), 6.98, 7.05 (each 1H, d, J=17.5 Hz, –CH=CH–), 7.22 (1H, tt, J=8, 2 Hz, H-4′), 7.32 (2H, td, J=8, 2 Hz, H-3′,5′), 7.50 (2H, br d, J=8 Hz, H-2′,6′). This was identical with pinosylvin.[2b]

(*E*)-3-Hydroxy-5-methoxystilbene (*O*-Methylpinosylvin) (**27**): Colorless needles from hexane–ether. ^{1}H-NMR ($CDCl_3$): 3.70 (3H, s, OMe), 5.38 (1H, br s, OH), 6.25 (1H, t, J=2 Hz, H-4), 6.52 (1H, t, J=2 Hz, H-2), 6.57 (1H, t, J=2 Hz, H-6), 6.88, 6.96 (each 1H, d, J=16 Hz, –CH=CH–), 7.16 (1H, tt, J=8, 2 Hz, H-4′), 7.26 (2H, td, J=8, 2 Hz, H-3′,5′), 7.30 (2H, dd, J=8, 2 Hz, H-2′,6′). This was identical with pinosylvin monomethyl ether.[2b]

(*E*)-2,2′-Dihydroxystilbene (**28**): Colorless needles from hexane–ether. ^{1}H-NMR: 6.78 (2H, dd, J=8, 2 Hz, H-3,3′), 6.80 (2H, td, J=8, 2 Hz, H-4,4′), 7.05 (2H, td, J=8, 2 Hz, H-5,5′), 7.46 (2H, s, –CH=CH–), 7.57 (2H, dd, J=8, 2 Hz, H-6,6′).

(*E*)-2,4′-Dihydroxystilbene (**29**): Colorless needles from hexane–ether. ^{1}H-NMR: 6.73 (2H, d, J=9 Hz, H-3′,5′), 6.74—6.83 (2H, m, H-3,5), 7.03 (1H, td, J=8, 2 Hz, H-5), 7.06, 7.28 (each 1H, d, J=16.5 Hz, –CH=CH–), 7.36 (2H, d, J=9 Hz, H-2′,6′), 7.49 (1H, dd, J=8, 2 Hz, H-6). *Anal.* Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.00; H, 5.69.

(*E*)-3,3′-Dihydroxystilbene (**30**): Colorless needles from hexane–acetone. ^{1}H-NMR: 6.68 (2H, ddd, J=8, 2, 1 Hz, H-4,4′), 6.95 (2H, dd, J=2, 1 Hz, H-2,2′), 6.99 (2H, ddd, J=8, 1.5, 1 Hz, H-6,6′), 7.03 (2H, s, –CH=CH–), 7.15 (2H, t, J=8 Hz, H-5,5′). *Anal.* Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.99; H, 5.85.

(*E*)-3,4′-Dihydroxystilbene (**31**): Colorless needles from hexane–ether. ^{1}H-NMR: 6.63 (1H, ddd, J=8, 3, 1 Hz, H-4), 6.78 (2H, d, J=9 Hz, H-3′,5′), 6.88, 7.01 (each 1H, d, J=16 Hz, –CH=CH–), 6.93 (1H, t, J=3 Hz, H-2), 6.96 (1H, br d, J=8 Hz, H-6), 7.12 (1H, t, J=8 Hz, H-5), 7.37 (2H, d, J=9 Hz, H-2′,6′). *Anal.*Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.20; H, 5.75.

(*E*)-4,4′-Dihydroxystilbene (**32**): Colorless needles from hexane–acetone. ^{1}H-NMR: 6.75 (4H, d, J=8 Hz, H-3,5,3′,5′), 6.90 (2H, s, –CH=CH–), 7.35 (4H, d, J=8 Hz, H-2,6,2′,6′).

(*E*)-3,4′,5-Trihydroxystilbene (**33**): Colorless needles from hexane–acetone. ^{1}H-NMR: 6.15 (1H, t, J=2 Hz, H-4), 6.44 (2H, d, J=2 Hz, H-2,6), 6.75 (2H, d, J=8 Hz, H-3′,5′), 6.77, 6.95 (each 1H, d, J=16 Hz, –CH=CH–), 7.37 (2H, d, J=8 Hz, H-2′,6′).

(*E*)-3,3′,5,5′-Tetrahydroxystilbene (**34**): Colorless needles from hexane–acetone. ^{1}H-NMR: 6.17 (2H, s, –CH=CH–), 6.44 (4H, s, H-2,6,2′,6′), 6.84 (2H, s, H-4,4′).

(*E*)-2,4-Dihydroxystilbene (35), (*E*)-2-Hydroxy-4-methoxystilbene (36), and (*E*)-2-Hydroxy-6-methoxystilbene (37) Benzyltriphenylphosphonium bromide (1.2 mol eq) was stirred with *tert*-BuOK (2 mol eq) in THF (20 ml) at −10 °C and the appropriate hydroxybenzaldehyde (200 mg) was added to the reaction mixture. The whole was stirred for 30 min, poured into water, neutralized with 1 N HCl, and extracted with AcOEt. The AcOEt layer was washed with brine, dried, and evaporated. The residue was purified by column chromatography to yield the respective (*E*)-stilbene.

(*E*)-2,4-Dihydroxystilbene (**35**): Yield 18%. Colorless needles from hexane–ether, mp 183—185 °C. ^{1}H-NMR (500 MHz, CD_3OD): 6.30 (1H, d, J=2 Hz, H-3), 6.32 (1H, dd, J=9, 2 Hz, H-5), 6.97, 7.37 (each 1H, d, J=17 Hz, –CH=CH–), 7.15 (1H, tt, J=8, 1 Hz, H-4′), 7.28 (2H, t, J=8 Hz, H-3′,5′), 7.35 (1H, d, J=9 Hz, H-6), 7.47 (2H, br d, J=8 Hz, H-2′,6′). MS: 212 (M^+, 100). *Anal.* Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.32; H, 5.79.

(*E*)-2-Hydroxy-4-methoxystilbene (**36**): Yield 58%. Colorless needles from hexane–ether, mp 123—124 °C. ^{1}H-NMR (500 MHz): 3.75 (3H, s, OMe), 6.40 (1H, d, J=2 Hz, H-3), 6.45 (1H, dd, J=9, 3 Hz, H-5), 7.02, 7.38 (each 1H, d, J=17 Hz, –CH=CH–), 7.17 (1H, tt, J=8, 1 Hz, H-4′), 7.30 (2H, t, J=8 Hz, H-3′,5′), 7.40 (1H, d, J=9 Hz, H-6), 7.45 (2H, dd, J=8, 1 Hz, H-2′,6′). MS: 226 (M^+, 100). HRMS m/z (M^+): Calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0958.

(*E*)-2-Hydroxy-6-methoxystilbene (**37**): Yield 84%. Colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.86 (3H, s, OMe), 5.50 (1H, br s, OH), 6.50 (1H, d, J=8 Hz, H-3), 6.60 (1H, d, J=8 Hz, H-5), 7.09 (1H, t, J=8 Hz, H-4), 7.19, 7.30 (each 1H, d, J=17 Hz, –CH=CH–), 7.28 (1H, tt, J=7.5, 1 Hz, H-4′), 7.37 (2H, t, J=7.5 Hz, H-3′,5′), 7.52 (2H, br d, J=7.5 Hz, H-2′,6′). MS: 226 (M^+, 100). HRMS m/z (M^+): Calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0997.

(*E*)-6-Allyloxy-2-hydroxystilbene (38) 6-Allyloxy-2-hydroxybenzaldehyde[11] was prepared in 68% yield by monoallylation of 2,6-dihydroxybenzaldehyde. This compound (60 mg) was added to a stirred mixture of benzyltriphenylphosphonium bromide (1.2 mol eq) and *tert*-BuOK (3 mol eq) in THF (15 ml) at room temperature. After 8 h, the mixture was poured into water and extracted with AcOEt. Purification of the product by column chromatography gave (*E*)-6-allyloxy-2-hydroxystilbene (**38**) (40 mg, 47%) as an oil. ^{1}H-NMR (500 MHz): 4.58 (2H, dt, J=5, 2 Hz, –OC$\underline{H}_2$CH=CH$_2$), 5.28, 5.43 (each 1H, dq, J=10, 2 and 17, 2 Hz, respectively, –OCH$_2$CH=C$\underline{H}_2$), 5.50 (1H, br s, OH), 6.03 (1H, ddt, J=17, 10, 5 Hz, –OCH$_2$C$\underline{H}$=CH$_2$), 6.49 (1H, d, J=8 Hz, H-3), 6.55 (1H, d, J=8 Hz, H-5), 7.06 (1H, t, J=8 Hz, H-4), 7.22, 7.30 (each 1H, d, J=17 Hz, –CH=CH–), 7.26 (1H, t, J=8 Hz, H-4′), 7.35 (2H, t, J=8 Hz, H-3′,5′), 7.52 (2H, d, J=8 Hz, H-2′,6′). MS: 252 (M^+, 100). HRMS m/z (M^+): Calcd for $C_{17}H_{16}O_2$: 252.1251. Found: 252.1173.

(*E*)-2,6-Dihydroxystilbene (41) A mixture of 2,6-dihydroxybenzaldehyde (200 mg), *tert*-butyldimethylsilyl chloride (1.2 mol eq) and imidazole (2.5 mol eq) in dimethylformamide (2 ml) was stirred at room temperature for 1 h. The mixture was poured into water and extracted with AcOEt, then the extract was dried and concentrated. The residue was purified by column chromatography to yield 6-*tert*-butyldimethylsilyloxy-2-hydroxybenzaldehyde (**39**, 162 mg, 44%), as an oil. ^{1}H-NMR (500 MHz): 0.30 (6H, s, Me_2Si), 1.00 (9H, s, *tert*-BuSi), 6.30 (1H, d, J=9 Hz, H-3), 6.53 (1H, d, J=9 Hz, H-5), 7.30 (1H, t, J=9 Hz, H-4), 10.28 (1H, s, CHO), 11.78 (1H, s, OH). MS: 252 (M^+, 1), 195 (100).

This compound (160 mg) was added to a stirred mixture of benzyltriphenylphosphonium bromide (1.2 mol eq) and *tert*-BuOK (1.5 mol eq) in THF (20 ml) at room temperature. After 8 h, the reaction mixture was poured into ice-water, neutralized with 1 N HCl, and extracted with AcOEt. The AcOEt layer was washed with brine, dried, and concentrated. The residue was purified by column chromatography to yield (*E*)-6-*tert*-butyldimethylsilyloxy-2-hydroxystilbene (**40**, 26 mg, 13%) as an oil. ^{1}H-NMR (500 MHz): 0.22 (6H, s, Me_2Si), 1.00 (9H, s, *tert*-BuSi), 6.44 (1H, d, J=8 Hz, H-3), 6.54 (1H, d, J=8 Hz, H-5), 6.99 (1H, t, J=8 Hz, H-4), 7.17, 7.27 (each 1H, d, J=18 Hz, –CH=CH–), 7.25 (1H, t, J=7.5 Hz, H-4′), 7.37 (2H, t, J=7.5 Hz, H-3′,5′), 7.50 (2H, d, J=7.5 Hz, H-2′,6′). MS: 326 (M^+, 21), 269 (100).

This compound (26 mg) in THF (10 ml) was stirred with TBAF (2 mol eq) at 0 °C for 10 min. The mixture was poured into water and extracted with AcOEt. The AcOEt layer was washed with brine, dried, and concentrated. The product was purified by column chromatography to

yield (*E*)-2,6-dihydroxystilbene (**41**, 18 mg, 100%) as colorless needles from hexane–ether, mp 106—107 °C. ^{1}H-NMR (500 MHz, CD_3OD): 6.32 (2H, d, J=8 Hz, H-3,5), 6.83 (1H, t, J=8 Hz, H-4), 7.15 (1H, t, J=8 Hz, H-4′), 7.29 (1H, t, J=8 Hz, H-3′,5′), 7.48 (2H, d, J=8 Hz, H-2′,6′), 7.49, 7.63 (each 1H, d, J=17 Hz, –CH=CH–). MS: 212 (M^+, 100). *Anal.* Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.19; H, 5.75.

(*E*)-5-Alkoxy-3-hydroxystilbenes (42—50) A mixture of (*E*)-3,5-dihydroxystilbene (**26**, 200 mg), potassium carbonate (1.5 mol eq) and alkyl bromide (1.5 mol eq) in dry acetone was refluxed for 3—7 h. The mixture was poured into water and extracted with ether. The organic layer was washed with brine, dried, and concentrated. The resulting mixture of dialkyl and monoalkyl derivatives was separated by chromatography. All monoalkyl derivatives (**42—50**) were crystallized as pale pink needles from hexane–ether and showed the following ^{1}H-NMR (270 MHz) spectra except for **44**: olefinic proton signals at δ 6.95—7.00 and 7.25 as doublets with J=17 Hz. Aromatic protons appeared at δ 6.32—6.35 (1H, t, J=2—3 Hz, H-4), 6.38—6.58 (1H, t, J=1.6—1.9 Hz, H-2), 6.64—6.68 (1H, t, J=1.6—1.9 Hz, H-6), 7.25—7.26 (1H, tt, J=7.3, 1.3—3 Hz, H-4′), 7.32—7.35 (2H, t, J=7.3 Hz, H-3′,5′), and 7.48—7.50 (2H, br d, J=7.3 Hz, H-2′,6′). The other data are listed in Table III.

(*E*)-5-Allyloxy-3-hydroxystilbene (**44**): ^{1}H-NMR: 4.53 (2H, dt, J=5, 2 Hz, $-OC\underline{H}_2CH=CH_2$), 5.29, 5.40 (each 1H, J=10, 2 Hz and 17, 2 Hz respectively, $-OCH_2CH=C\underline{H}_2$), 6.06 (1H, ddt, J=17, 10, 5 Hz, $-OCH_2C\underline{H}=CH_2$).

Demethylation of (*Z*)-3,5-Dimethoxystilbene (51) (*Z*)-3,5-Dimethoxystilbene (**51**) was separated from the (*E*/*Z*) mixture (see above) by repeated chromatography as an oil. ^{1}H-NMR (270 MHz): 3.63 (6H, s, OMe), 6.60 (1H, t, J=2.3 Hz, H-4), 6.39 (2H, d, J=2.3 Hz, H-2,6), 6.53, 6.63 (each 1H, d, J=12 Hz, –CH=CH–), 7.16—7.29 (5H, m, H-2′,3′,4′,5′,6′). MS: 240 (M^+, 100). HRMS m/z (M^+): Calcd for $C_{16}H_{16}O_2$: 240.1149. Found: 240.1138.

This compound (350 mg) was demethylated with BBr_3 (3 mol eq) in CH_2Cl_2 as described above to yield (*Z*)-3,5-dihydroxystilbene (**52**, 228 mg, 45%) and (*Z*)-3-hydroxy-5-methoxystilbene (**53**, 69 mg, 21%). These were separated by column chromatography.

(*Z*)-3,5-Dihydroxystilbene (**52**): Colorless oil. ^{1}H-NMR (400 MHz): 5.74 (2H, br s, 2×OH), 6.20 (1H, t, J=2 Hz, H-4), 6.29 (2H, d, J=2 Hz, H-2,6), 6.44, 6.56 (each 1H, d, J=12 Hz, –CH=CH–), 7.18 (1H, tt, J=7, 1 Hz, H-4′), 7.22 (2H, t, J=7 Hz, H-3′,5′), 7.25 (2H, dd, J=7, 1 Hz, H-2′,6′). MS: 212 (M^+, 100). HRMS m/z (M^+): Calcd for $C_{14}H_{12}O_2$: 212.0837. Found: 212.0792.

(*Z*)-3-Hydroxy-5-methoxystilbene (**53**): Colorless oil. ^{1}H-NMR (400 MHz): 3.64 (3H, s, OMe), 6.25 (1H, t, J=2 Hz, H-4), 6.29 (1H, br s, H-2), 6.37 (1H, br s, H-6), 6.48, 6.60 (each 1H, d, J=12 Hz, –CH=CH–), 7.17—7.30 (5H, m, H-2′,3′,4′,5′,6′). MS: 226 (M^+, 100). HRMS m/z (M^+): Calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0997.

2,4-Dihydroxybibenzyl (57), 2,6-Dihydroxybibenzyl (58), and 2,4,6-Trihydroxybibenzyl (59) Methoxystilbenes (**8**, **10**, and **16**, each 100 mg) in ethanol (20 ml) were each hydrogenated over 10% Pd–C (50 mg) for 1 h. After removal of the catalyst and the solvent, the product was purified by column chromatography to yield the corresponding bibenzyl.

2,4-Dimethoxybibenzyl (**54**): Yield 99%. Colorless oil. ^{1}H-NMR (270 MHz): 2.83 (4H, s, $-CH_2CH_2-$), 3.97 (6H, s, 2×OMe), 6.40 (1H, dd, J=8.3, 2 Hz, H-5), 6.44 (1H, d, J=2 Hz, H-3), 6.96 (1H, d, J=8.3 Hz, H-6), 7.12—7.35 (5H, m, H-2′,3′,4′,5′,6′). MS: 242 (M^+, 9), 151 (100), 91 (11).

2,6-Dimethoxybibenzyl (**55**): Yield 99%. Colorless needles from hexane–ether, mp 54—55 °C. ^{1}H-NMR (270 MHz): 2.76, 2.92 (each 2H, t, J=7.3 Hz, $-CH_2CH_2-$), 3.75 (6H, s, 2×OMe), 6.53 (2H, d, J=9 Hz, H-3,5), 7.13 (1H, t, J=9 Hz, H-4), 7.17—7.29 (5H, m, H-2′,3′,4′,5′,6′). MS: 242 (M^+, 47), 151 (100), 91 (61).

2,4,6-Trimethoxybibenzyl (**56**): Yield 99%. Colorless needles from hexane–ether, mp 52—53 °C. ^{1}H-NMR (270 MHz): 2.60—2.83 (4H, m, $-CH_2CH_2-$), 3.75 (9H, 3×OMe), 6.20 (2H, s, H-3,5), 7.07—7.20 (5H, m, H-2′,3′,4′,5′,6′). MS: 272 (M^+, 6), 181 (100), 136 (15), 121 (15).

The above methoxybibenzyls were demethylated with BBr_3 (3 mol eq) as described above to yield the hydroxybibenzyls.

2,4-Dihydroxybibenzyl (**57**): Yield 78%. Colorless needles from hexane–ether, mp 137—138 °C. ^{1}H-NMR (270 MHz, CD_3OD): 2.68—2.85 (4H, m, $-CH_2CH_2-$), 6.17 (1H, dd, J=8.3, 2 Hz, H-5), 6.28 (1H, d, J=2 Hz, H-3), 7.73 (1H, d, J=8.3 Hz, H-6), 7.06—7.27 (5H, m, H-2′,3′,4′,5′,6′). MS: 214 (M^+, 16), 123 (100). *Anal.* Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.42; H, 6.61.

2,6-Dihydroxybibenzyl (**58**): Yield 94%. Colorless needles from hexane–ether, mp 127—128 °C. ^{1}H-NMR (500 MHz, CD_3OD): 2.74—2.87 (4H, m, $-CH_2CH_2-$), 6.30 (2H, d, J=8 Hz, H-3,5), 6.80 (1H, t, J=8 Hz, H-4), 7.10 (1H, tt, J=7, 2 Hz, H-3′), 7.21—7.32 (4H, m, H-2′,3′,5′,6′). MS: 214 (M^+, 28), 123 (100). *Anal.* Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.55; H, 6.64.

2,4,6-Trihydroxybibenzyl (**59**): Yield 79%. Colorless needles from hexane–ether, mp 166—168 °C (lit. mp 159—160 °C).[12] ^{1}H-NMR (500 MHz, CD_3OD): 2.69—2.77 (4H, m, $-CH_2CH_2-$), 5.86 (2H, s, H-3,5), 7.09—7.32 (5H, m, H-2′,3′,4′,5′,6′). MS: 230 (M^+, 10), 139 (100).

3,5-Dihydroxybibenzyl (60) and 3-Hydroxy-5-methoxybibenzyl (61) (*E*)-3,5-Dihydroxystilbene (**26**) and its methyl ether (**27**) (each 200 mg) in ethanol (50 ml) were each hydrogenated over 10% Pd–C (50 mg) for 1 h to yield **60** and **61**.

3,5-Dihydroxybibenzyl (**60**): Yield 97%. Colorless needles from hexane–ether, mp 84—85 °C. ^{1}H-NMR (400 MHz): 2.73—2.90 (4H, $-CH_2CH_2-$), 5.45 (2H, br s, OH), 6.19 (1H, t, J=2 Hz, H-4), 6.24 (2H, d, J=2 Hz, H-2,6), 7.10—7.20 (3H, m, H-2′,4′,6′), 7.25 (2H, t, J=7.5 Hz, H-3′,5′). MS: 214 (M^+, 55), 123 (67), 91 (100). *Anal.* Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.58; H, 6.59.

3-Hydroxy-5-methoxybibenzyl (**61**): Yield 99%. Colorless needles from hexane, mp 54—55 °C (lit. 50—52 °C).[13] ^{1}H-NMR (400 MHz): 2.78—2.92 (4H, m, $-CH_2CH_2-$), 3.74 (3H, s, OMe), 4.93 (1H, br s, OH), 6.23 (1H, t, J=2 Hz, H-2), 6.25 (1H, J=2 Hz, H-6), 6.32 (1H, t, J=2 Hz, H-4), 7.15—7.20 (3H, m, H-2′,4′,6′), 7.27 (2H, t, J=7 Hz, H-3′,5′). MS: 228 (M^+, 69), 137 (100).

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