Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 11070–11077

An unusual, mild and convenient one-pot two-step access to (*E*)-stilbenes from hydroxy-substituted benzaldehydes and phenylacetic acids under microwave activation: a new facet of the classical Perkin reaction☆

Arun K. Sinha,* Vinod Kumar, Abhishek Sharma, Anuj Sharma and Rakesh Kumar

Natural Plant Products Division, Institute of Himalayan Bioresource Technology, Palampur 176061, Himachal Pradesh, India

Received 10 May 2007; revised 24 July 2007; accepted 10 August 2007
Available online 15 August 2007

Abstract—A mild and convenient one-pot two-step synthesis of hydroxystilbenes with trans selectivity has been developed through a modified Perkin reaction between benzaldehydes and phenylacetic acids bearing 4- or 2-hydroxy substitution at the aromatic ring, in the presence of piperidine–methylimidazole and polyethylene glycol under microwave irradiation. The observation of a simultaneous condensation–decarboxylation leading to the unusual formation of hydroxystilbenes in lieu of α-phenylcinnamic acid reveals an interesting facet to the classical Perkin reaction. The developed protocol provides a green alternative to the prevalent methods employing a toxic decarboxylating agent in the form of quinoline/Cu salt, and the requirement for harsh protection–deprotection steps for the synthesis of hydroxylated stilbenes.

1. Introduction

Hydroxylated stilbenes constitute an important class of natural compounds due to their wide-ranging biological activities,[1] putative potential as nutraceuticals[2] as well as their application in molecular photonics and optoelectronics.[3] For instance, resveratrol (3,4′,5-trihydroxy-(*E*)-stilbene), a major component of red wine, has been implicated as a potent cardio protective agent thus lending credence to the conjecture that red wine consumption retards cardiovascular mortality.[4] In addition, resveratrol has been shown to act as an effective AhR antagonist thus indicating its therapeutic significance against fatal conditions like cancer and AIDS.[5] Similarly, pterostilbene has been widely used in the treatment of diabetes and as an antitumour agent.[6] A number of subsequent investigations have also disclosed the wide-ranging applications of many other stilbenes.[7] The remarkable biological and industrial importance of hydroxylated (*E*)-stilbenes has prompted intensive efforts towards development of their synthetic methodologies. Thus, hydroxylated stilbenes have been accessed through various synthetic approaches[8] including Knoevenagel–Doebner, Heck, Wittig, Suzuki and Perkin reactions, etc. Amongst the prevalent synthetic approaches towards these bioactive stilbenes, the Perkin reaction between benzaldehydes and phenylacetic acids in the presence of acetic anhydride and a base followed by decarboxylation with quinoline–Cu salt has remained a prominent method[9] since its pioneering application towards the synthesis[10] of resveratrol in 1941. Subsequently, some other reports describing the synthesis of stilbenes through a modified Perkin reaction[11] have also emerged. Recently, a reinvestigation of the Perkin reaction has been reported wherein factors governing the synthesis of *cis*/*trans* α-phenylcinnamic acids[12] followed by decarboxylation into the corresponding stilbene have been examined. Despite their utility, all of the above modifications to the Perkin reaction primarily disclose a multistep approach involving sequential protection, condensation, decarboxylation and deprotection steps for the synthesis of hydroxylated stilbenes. Evidently, the development of a simple and convenient synthetic methodology for hydroxylated stilbenes has been severely constrained by the extreme susceptibility of the hydroxyl function towards polymerization[13] thus necessitating the tedium of harsh protection–deprotection steps. In addition, the indispensable requirement of toxic quinoline–Cu combination[14] for decarboxylation of α-phenylcinnamic acids coupled with a low overall yield (20–40%)[14] of stilbenes at times limits the environmental sustainability and synthetic utility of the common variants of the Perkin reaction.

The above contemporary concerns attracted our attention and herein we disclose a new facet to the classical Perkin reaction through a convenient and environmentally benign

☆ IHBT Communication No: 0677.
Keywords: (*E*)-Stilbenes; Perkin reaction; Decarboxylation; C–C coupling; Microwave.
* Corresponding author. Tel.: +91 1894 230426; e-mail: aksinha08@rediffmail.com

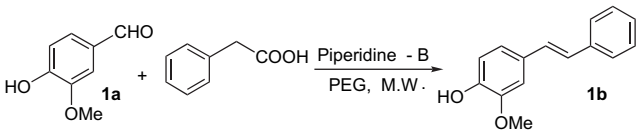
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.08.034

one-pot two-step synthesis of hydroxylated (*E*)-stilbenes from 4- or 2-hydroxy-substituted benzaldehydes and phenylacetic acids under microwave irradiation.

2. Results and discussion

As part of our ongoing interest in microwave-induced synthesis of important bioactive compounds,[15] we had a successful precedent in the one-pot, two-step synthesis of FEMA-GRAS approved hydroxy styrenes via condensation of the corresponding hydroxy benzaldehydes with malonic acid in the presence of an acetic acid–piperidine combination.[16b] In the context of our current efforts to devise a mild and convenient synthetic route for bioactive hydroxylated stilbenes, we were intrigued by the possibility of utilizing our previously explored acetic acid–piperidine combination[16] towards a microwave-induced one-pot synthesis of stilbenes through a Perkin type reaction between hydroxy benzaldehydes and phenylacetic acids. Consequently, a mixture of vanillin (4-hydroxy-3-methoxybenzaldehyde) (**1a**) and phenylacetic acid (1.2 equiv) was irradiated under microwaves for 20 min in the presence of acetic acid (7 equiv)–piperidine (2 equiv). However, the method provided the expected stilbene in only traces along with unreacted starting material and several side-products. The above result led us to reason that unlike our earlier study,[16b] the use of acetic acid might not be compatible for the condensation between benzaldehyde (**1a**) and phenylacetic acid in view of the fact that the latter is a comparatively weaker active methylene compound than malonic acid (pK_a=2.83). Consequently, the above reaction between **1a** and phenylacetic acid (1.2 equiv) was conducted in piperidine (5 equiv) alone and **1b** was obtained in 34% yield along with the corresponding α-phenylcinnamic acid and unreacted starting material. Replacement of piperidine with other bases such as triethylamine, pyridine, collidine and imidazole was not found to be suitable for further enhancement in the yield of **1b**. Encouraged by the above result with piperidine, we decided to evaluate the effect of various high-boiling point solvents on the yield of the condensation–decarboxylation product **1b**, since decarboxylation is generally known to occur at high reaction temperatures.[17] Consequently, a range of solvents including DMF, DMSO, PEG and DEG were examined for the above reaction in the presence of piperidine as a base. Amongst these, PEG was found to be the optimum solvent under the given reaction conditions (40% yield). In our quest to further increase the yield of **1b**, we searched for various options. In particular, the use of a combination of two bases appeared interesting to us especially since a number of earlier reports[18] have demonstrated the efficacy of such a combination. In this context, a combination of piperidine with imidazole seemed to be an attractive option in view of the remarkable ability of imidazole[19] to efficiently absorb microwave energy due to the formation of a polar imidazolium salt of the aryl acid intermediate. Thus, **1a** and phenylacetic acid were treated in the presence of a combination of piperidine–imidazole (1.5 equiv each) in PEG. Gratifyingly, the yield of **1b** was found to be enhanced by up to 49%. In order to further increase the yield of **1b**, we explored the dependence of yield on structural changes in the imidazole moiety. Interestingly, methylimidazole (Mim, Table 1, entry 2) was found to augment the yield of **1b** to 56% while histidine (entry 3) and 1-butyl-3-methylimidazolium chloride (entry 4) provided **1b** in an inferior yield. Subsequently, various combinations of piperidine with other bases were screened but none of these were found to be suitable (Table 1).

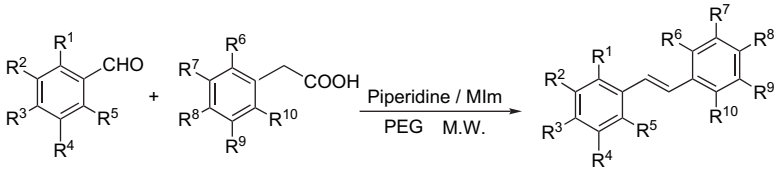
Table 1. Effect of different base combinations on the synthesis of **1b** from **1a** under microwave irradiation[a]



S. No.	Base (B)	Yield (%)
1	Imidazole	49
2	Methylimidazole	56
3	Histidine	28
4	1-Butyl-3-methylimidazoliumchloride	35
5	Pyridine	47
6	Triethylamine	43
7	Collidine	43

[a] CEM Discover monomode microwave. Conditions: MW (150 W, 160 °C); 4-hydroxy-3-methoxybenzaldehyde (6.5 mmol); phenylacetic acid (7.2 mmol); piperidine (9.8 mmol); PEG (4–5 mL); base (9.8 mmol).

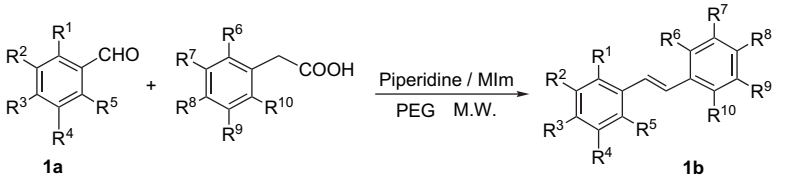
After the success of **1b**, the developed method (Scheme 1) was extended to various other hydroxy-substituted benzaldehydes and phenylacetic acids as summarized in Table 2. It is evident from Table 2 that a 4- or 2-hydroxy substitution in either the benzaldehyde or the phenylacetic acid provides a favourable condition for the one-pot two-step synthesis of stilbenes. Thus, **2b** and **3b** were obtained in 54% and 44% yields, respectively, depending upon 4-hydroxy substitution at benzaldehyde or phenylacetic acid. Similarly, the 2-hydroxy-substituted substrates (entry 12 and entry 13) were also found to be amenable towards the above reaction; however, the corresponding stilbenes



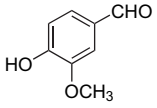
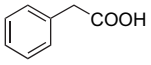
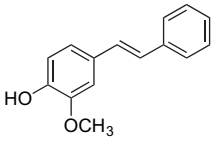
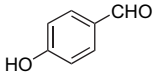
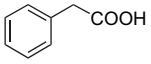
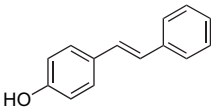
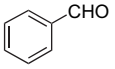
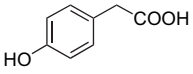
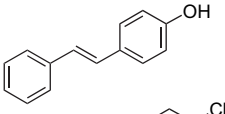
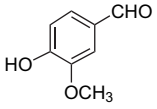
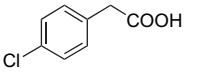
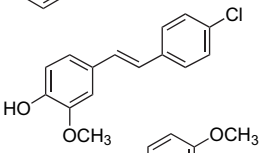
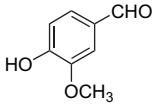
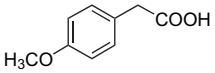
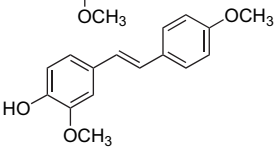
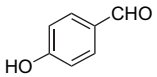
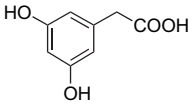
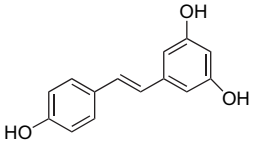
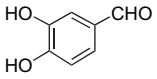
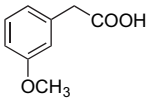
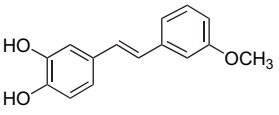
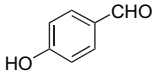
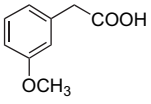
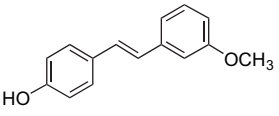
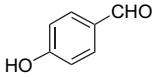
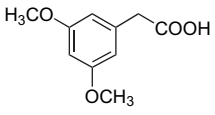
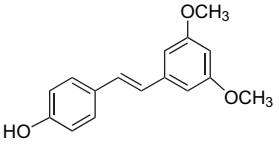
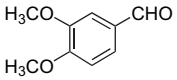
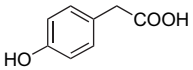
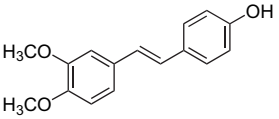
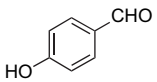
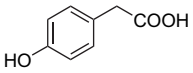
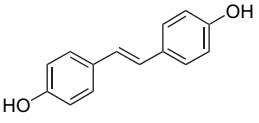
where
at least one of R^1or R^3or R^5or R^6 or R^8 or R^{10} = OH
and R^1-R^{10} = H, OMe, OH, Cl etc.

Scheme 1.

Table 2. Synthesis of hydroxylated (*E*)-stilbenes (**1b–17b**) under microwave irradiation[a]

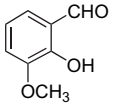
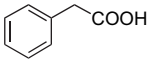
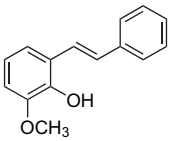
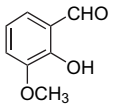
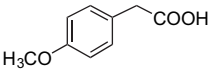
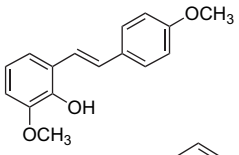
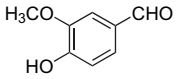
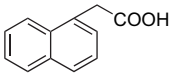
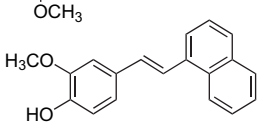
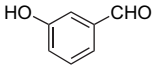
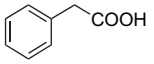
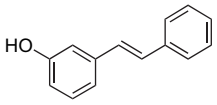
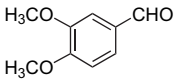
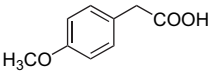
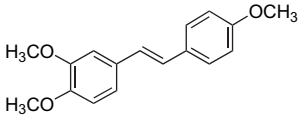
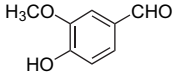
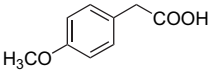
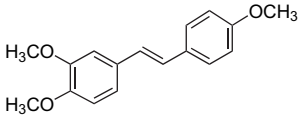


1a **1b**

S. No.	Benzaldehydes (a)	Phenylacetic acids	Reaction time (min)	Product (b)	yield[b] (%)	Ref.
1			10		56	8a,24a
2			10		54	8b,24e
3			10		44	24a,e
4			10		71[d]	
5			10		53[d]	
6			10		51	7b,24g
7			10		54	24d
8			10		56[d]	
9			10		64	6b
10			10		41[d]	
11			10		46	24a,c

(*continued*)

Table 2. (*continued*)

S. No.	Benzaldehydes (a)	Phenylacetic acids	Reaction time (min)	Product (b)	yield[b] (%)	Ref.
12			10		41	24b
13			12		43[d]	
14			12		44[d]	
15			30		nd	
16			30		Traces	24f
17			40		42[c]	24f

[a] CEM Discover monomode microwave.
[b] Benzaldehyde (6.5 mmol), phenylacetic acid (7.2 mmol), Mim (9.8 mmol), piperidine (9.8 mmol) and PEG (4–5 mL) under microwave for 10–30 min (150 W, 160 °C).
[c] After the formation of stilbene as described in footnote b, dimethyl sulfate (26 mmol) was added to the same pot and the mixture irradiated with microwave for 30 min.
[d] Spectral data of these novel compounds are given in Section 4.

were obtained in comparatively lower yield along with the formation of some side-products including coumarin derivatives. Interestingly, an enhanced yield of stilbene (entry 4) was obtained in the case when an electron-withdrawing substituent (e.g., Cl) was present in the *para* position of the corresponding phenylacetic acid. The foregoing result is evidently in accordance with the Hammett equation[20] as well as the proposed mechanism, whereby electron withdrawal by the Cl group stabilizes the incipient carbanion of phenylacetic acid. Similarly, the presence of an electron donating group (OMe) at the *meta* position (entry 9) of phenylacetic acid led to an improved performance of the reaction as compared to the case when the methoxy group was present at the *para* position (entry 5). The foregoing success with 4-hydroxylated stilbenes led us to explore the developed method towards the synthesis of some biologically important methoxylated stilbenes[21] from the corresponding methoxylated benzaldehydes. However, the method provided the corresponding stilbene (entry 16) only in traces. Nevertheless, in pursuit of our endeavour to extend the developed method towards the synthesis of methoxylated stilbenes, we chose to explore a hitherto unprecedented one-pot, three-step condensation–decarboxylation–methylation reaction. Consequently, **1a** was reacted with 4-methoxyphenylacetic acid in the presence of piperidine–Mim and PEG under microwave irradiation and upon formation of stilbene, dimethyl sulfate was added. To our delight, the method led to the synthesis of the desired methoxylated stilbene (entry 17b) in 42% yield.

We envisage that a new mechanistic pathway might underlie the peculiar simultaneous condensation–decarboxylation observed in our case (Fig. 1). Thus, we hypothesize that Mim initially forms a carboxylate salt with the aryl acid intermediate obtained by the piperidine-induced condensation between hydroxy-substituted benzaldehydes and phenylacetic acids. The polar Mim carboxylate salt subsequently helps in the efficient absorption of microwave energy thus facilitating the piperidine-induced formation of *para*-quinone methide. Consequently, the *para*-quinone methide eliminates a molecule of carbon dioxide to ensure the formation of stilbene. Further investigations regarding the elucidation of the precise mechanism are currently under progress.

In order to ascertain the specific role of microwave irradiation, **1a** and phenylacetic acid were reacted in the presence of piperidine–methylimidazole and PEG under conventional heating at reflux temperature for 6–8 h. However, the corresponding α-phenylcinnamic acid was obtained as the major product (62%) along with **1b** in 21% yield, thus unequivocally demonstrating the role of microwave in effectively

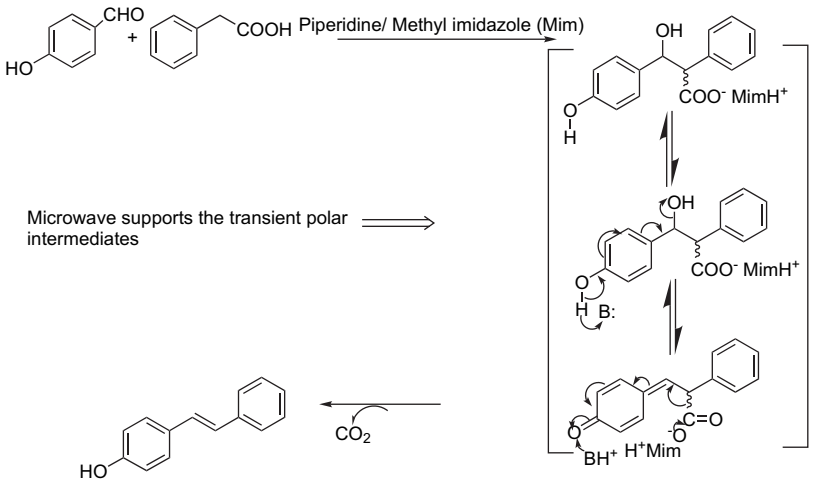


Figure 1.

bringing about the simultaneous condensation–decarboxylation of **1a**. The remarkable ability of microwaves to facilitate polar reactions has been well recognized.[22] Presumably, such a microwave effect facilitates the simultaneous condensation–decarboxylation observed in our case, especially in view of the fact that all the intermediates proposed in the mechanism are more polar[22] than the starting material.

Our premise of simultaneous condensation–decarboxylation was proved when the treatment of α-phenyl 4-hydroxycinnamic acid with piperidine and methylimidazole under microwave irradiation provided the product stilbene in inferior yield.

It may be mentioned here that the venerable Perkin reaction has been widely recognized for the synthesis of a variety of cinnamic acid derivatives from the corresponding benzaldehydes including hydroxy benzaldehydes and phenylacetic acid in the presence of acetic anhydride–triethylamine.[9] However, the developed method[23] reveals for the first time, a new facet to the classical Perkin reaction through the occurrence of an unusual microwave-induced and base-catalyzed simultaneous condensation–decarboxylation effect leading to the direct synthesis of bioactive hydroxylated stilbenes from the corresponding hydroxy-substituted benzaldehydes and phenylacetic acids.

3. Conclusion

In conclusion, a new facet to the classical Perkin reaction is disclosed whereby an unusual simultaneous condensation–decarboxylation provides a mild and convenient one-pot access to various bioactive stilbenes from hydroxy-substituted benzaldehydes and phenylacetic acids under microwave irradiation. In addition, the method is extended towards the formation of some important methoxylated analogues of hydroxystilbenes via an unprecedented one-pot condensation–decarboxylation–methylation process. The developed protocol affords a green alternative to the prevalent methods employing toxic quinoline–Cu salt and harsh protection–deprotection agents.

4. Experimental section

4.1. General method

All the chemicals were obtained from commercial sources (Merck and Acros) and were used without further purification. ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. CEM Discover© focused microwave (2450 MHz, 300 W) was used wherever mentioned. HRMS spectra were determined using micromass Q-TOF ultima spectrometer.

4.2. Synthesis of stilbenes under focused microwave irradiation

A mixture of substituted benzaldehyde (**1a–17a**) (6.5 mmol), phenylacetic acid derivative (7.2 mmol), methylimidazole (9.8 mmol), piperidine (9.8 mmol) and polyethylene glycol (4–5 mL) was taken in a 100 mL round bottom flask. The flask was shaken well and irradiated under focused monomode microwave system (150 W, 160 °C) fitted with reflux condenser for the time given in Table 2. After the completion of reaction, the reaction mixture was cooled and acidified with dil HCl (pH=5). Then the aqueous layer was extracted with ethyl acetate (2×20 mL) and the organic layer was dried over sodium sulfate and vacuum distilled to obtain crude product, which was further purified by column chromatography using Si gel (60–120 mesh size) with a 1:5 mixture of ethyl acetate and hexane to give the pure stilbene whose spectral data matched well with the reported values.[6,14,24]

4.3. One-pot three-step condensation–decarboxylation–methylation for the synthesis of methoxystilbenes

A mixture of substituted 4-hydroxy-3-methoxybenzaldehyde (**1a**) (6.5 mmol), 4-methoxyphenylacetic acid (7.2 mmol), methylimidazole (9.8 mmol), piperidine (9.8 mmol) and polyethylene glycol (4–5 mL) was taken in a 100 mL round bottom flask. The flask was shaken well and irradiated under focused monomode microwave system (150 W, 160 °C) fitted with reflux condenser for 10 min. After the formation of hydroxy stilbene, dimethyl

sulfate (26.0 mmol) was added in the same pot and reaction mixture again irradiated in microwave for 30 min. Thereafter, the reaction mixture was cooled and acidified with dil HCl (pH=5). Then the aqueous layer was extracted with ethyl acetate (2×20 mL) and the organic layer was dried over sodium sulfate and vacuum distilled to obtain crude product, which was further purified by column chromatography using Si gel (60–120 mesh size) with a 1:5 mixture of ethyl acetate and hexane to give the pure stilbene in 42% yield.

4.4. Supporting information available

Spectral data of some representative stilbenes.

4.4.1. 4-Hydroxy-3-methoxystilbene (Table 2/1b).[8a,24a] White solid (mp 132–134 °C; lit.[8a] mp 134 °C); δ_H (300 MHz, $CDCl_3$) 7.45 (2H, d, *J* 7.4 Hz), 7.32–7.27 (2H, m), 7.21–7.16 (1H, m), 7.02–6.85 (5H, m), 5.66 (1H, s), 3.89 (3H, s); δ_C (75.4 MHz, $CDCl_3$) 146.7, 145.6, 137.6, 130.0, 128.7, 127.2, 126.5, 126.2, 120.5, 114.6, 108.3 and 55.9. HREIMS data: *m/z* $[M+H]^+$ for $C_{15}H_{15}O_2$, calculated=227.2840; observed=227.2826.

4.4.2. 4-Hydroxystilbene (Table 2/2b and 3b).[8b,24e] White solid (mp 185–187 °C; lit.[8b] mp 186 °C); δ_H (300 MHz, $CDCl_3$) 7.40 (2H, d, *J* 7.6 Hz), 7.31 (2H, d, *J* 8.5 Hz), 7.24–7.19 (2H, m), 7.12 (1H, t, *J* 6.8 Hz), 7.01 (1H, d, *J* 16.7 Hz), 6.89 (1H, d, *J* 16.7 Hz), 6.72 (2H, d, *J* 8.5 Hz); δ_C (75.4 MHz, $CDCl_3$) 157.0, 137.9, 129.1, 128.2, 128.1, 127.5, 126.6, 125.8, 125.4 and 115.4.

4.4.3. 4-Chloro-4′-hydroxy-3′-methoxystilbene (Table 2/4b). White solid (mp 121–124 °C); δ_H (300 MHz, $CDCl_3$) 7.35 (2H, d, *J* 8.4 Hz), 7.25 (2H, d, *J* 8.0 Hz), 6.96–6.91 (3H, m), 6.87 (2H, d, *J* 8.0 Hz), 5.72 (1H, s), 3.87 (3H, s); δ_C (75.4 MHz, $CDCl_3$) 146.8, 145.8, 136.1, 132.7, 129.6, 129.2, 128.8, 127.4, 125.1, 120.6, 114.6, 108.3 and 55.9. HREIMS data: *m/z* $[M+H]^+$ for $C_{15}H_{14}O_2Cl$, calculated=261.7228; observed=261.7229.

4.4.4. 4-Hydroxy-3,4′-dimethoxystilbene (Table 2/5b). White crystalline solid (mp 163–166 °C); δ_H (300 MHz, $CDCl_3$) 7.36 (2H, d, *J* 8.4 Hz), 6.94–6.90 (2H, m), 6.83–6.80 (5H, m), 5.59 (1H, s), 3.86 (3H, s), 3.75 (3H, s); δ_C (75.4 MHz, $CDCl_3$) 159.0, 146.7, 145.2, 130.3, 127.4, 126.6, 126.1, 120.1, 114.5, 114.1, 108.0, 55.9 and 55.3. HREIMS data: *m/z* $[M+H]^+$ for $C_{16}H_{17}O_3$, calculated=257.3103; observed=257.3149.

4.4.5. 3,4′,5-Trihydroxystilbene (resveratrol) (Table 2/6b).[7b,24g] White crystalline solid (mp 256–259 °C; lit.[7b] mp 260 °C); δ_H (300 MHz, CD_3COCD_3) 7.37 (2H, d, *J* 8.0 Hz), 6.97 (1H, d, *J* 16.1 Hz), 6.84 (1H, d, *J* 16.1 Hz), 6.77 (2H, d, *J* 8.0 Hz), 6.51 (2H, s), 6.31 (1H, s); δ_C (75.4 MHz, CD_3COCD_3) 159.1, 157.5, 139.9, 129.4, 128.6, 128.2, 126.3, 115.9, 104.8 and 102.1.

4.4.6. 3,4-Dihydroxy-3′-methoxystilbene (Table 2/7b).[24d] White solid (mp 101–104 °C; lit.[24d] mp 102 °C); δ_H (300 MHz, CD_3COCD_3) 7.95 (1H, s), 7.85 (1H, s), 7.41–7.38 (2H, m), 7.01 (1H, s), 6.86–6.81 (5H, m), 6.75 (1H, d, *J* 8.0 Hz), 3.72 (3H, s); δ_C (75.4 MHz, CD_3COCD_3) 159.1, 145.2, 144.9, 130.6, 130.2, 127.3, 126.5, 125.3, 118.7, 115.3, 114.0, 112.7 and 54.6.

4.4.7. 4-Hydroxy-3′-methoxystilbene (Table 2/8b). White solid (mp 132–134 °C); δ_H (300 MHz, CD_3COCD_3) 8.46 (1H, s), 7.39 (2H, d, *J* 8.5 Hz), 7.20–7.13 (1H, m), 7.07–7.04 (3H, m), 6.97 (1H, d, *J* 16.1 Hz), 6.80 (2H, d, *J* 8.5 Hz), 6.74 (1H, d, *J* 7.1 Hz), 3.74 (3H, s); δ_C (75.4 MHz, CD_3COCD_3) 160.1, 157.4, 139.4, 129.5, 129.0, 128.7, 127.9, 125.5, 118.7, 115.5, 112.7, 111.3 and 54.6. HREIMS data: *m/z* $[M+H]^+$ for $C_{15}H_{15}O_2$, calculated=227.2840; observed=227.2812.

4.4.8. 4-Hydroxy-3′,5′-dimethoxystilbene (pterostilbene) (Table 2/9b).[6b] White crystalline solid (mp 85–87 °C; lit.[6b] mp 87–88 °C); δ_H (300 MHz, $CDCl_3$) 7.34 (2H, d, *J* 8.48 Hz), 6.99 (1H, d, *J* 16.5 Hz), 6.85 (1H, d, *J* 16.5 Hz), 6.78 (2H, d, *J* 8.4 Hz), 6.60 (2H, s), 6.33 (1H, s), 3.77 (6H, s); δ_C (75.4 MHz, $CDCl_3$) 160.9, 155.5, 139.7, 130.0, 128.8, 128.1, 126.5, 115.7, 104.5, 99.7 and 55.4. HREIMS data: *m/z* $[M+H]^+$ for $C_{16}H_{17}O_3$, calculated=257.3103; observed=257.3175.

4.4.9. 4-Hydroxy-3′,4′-dimethoxystilbene (Table 2/10b). White solid (mp 180–182 °C); δ_H (300 MHz, DMSO-d_6) 7.27 (2H, d, *J* 7.6 Hz), 7.04 (1H, s), 6.93 (2H, d, *J* 7.6 Hz), 6.84 (3H, m), 6.70 (1H, d, *J* 6.8 Hz), 3.79 (3H, s), 3.75 (3H, s); δ_C (75.4 MHz, DMSO-d_6) 156.7, 149.2, 148.5, 131.4, 129.3, 127.2, 126.4, 125.2, 119.2, 115.0, 112.1, 109.0 and 55.0. HREIMS data: *m/z* $[M+H]^+$ for $C_{16}H_{17}O_3$, calculated=257.3103; observed=257.3160.

4.4.10. 4,4′-Dihydroxystilbene (Table 2/11b).[24a,24c] White solid (mp 279–281 °C; lit.[24c] mp 278 °C); δ_H (300 MHz, MeOD) 7.27 (4H, d, *J* 8.4 Hz), 6.81 (2H, s), 6.6 (4H, d, *J* 8.4 Hz), δ_C (75.4 MHz, MeOD) δ 156.5, 129.6, 127.0, 125.3 and 115.0.

4.4.11. 2-Hydroxy-3-methoxystilbene (Table 2/12b).[24b] White solid (mp 85–87 °C); δ_H (300 MHz, $CDCl_3$) 7.51 (2H, d, *J* 7.6 Hz), 7.44 (1H, d, *J* 16.4 Hz), 7.38 (1H, d, *J* 16.4 Hz), 7.33 (1H, t, *J* 7.6 Hz), 7.22–7.11 (3H, m), 6.80 (1H, t, *J* 7.9 Hz), 6.73 (1H, d, *J* 7.9 Hz), 5.95 (1H, s), 3.84 (3H, s); δ_C (75.4 MHz, $CDCl_3$) 146.7, 143.5, 137.8, 129.3, 128.5, 127.3, 126.5, 123.7, 122.9, 119.5, 118.8, 109.4 and 56.0. HREIMS data: *m/z* $[M+H]^+$ for $C_{15}H_{15}O_2$, calculated=227.2840; observed=227.2830.

4.4.12. 2-Hydroxy-3,4′-dimethoxystilbene (Table 2/13b). White solid (mp 80–84 °C); δ_H (300 MHz, $CDCl_3$) 7.45 (2H, d, *J* 8.8 Hz), 7.29 (1H, d, *J* 16.1 Hz), 7.13 (1H, d, *J* 8.1 Hz), 7.11 (1H, d, *J* 16.1 Hz), 6.85–6.76 (3H, m), 6.71 (1H, d, *J* 7.6 Hz), 5.94 (1H, s), 3.83 (3H, s), 3.76 (3H, s); δ_C (75.4 MHz, $CDCl_3$) 159.1, 146.7, 143.2, 130.7, 128.9, 127.8, 124.0, 120.8, 119.5, 118.6, 114.0, 109.1, 56.3 and 55.3. HREIMS data: *m/z* $[M+H]^+$ for $C_{16}H_{17}O_3$, calculated=257.3103; observed=257.3116.

4.4.13. 1-(4′-Hydroxy-3′-methoxyphenyl)-2-naphthylethene (Table 2/14b). White solid (mp 83–86 °C); δ_H (300 MHz, $CDCl_3$) 8.22 (1H, d, *J* 7.6 Hz), 7.85 (1H, d, *J* 8.2 Hz), 7.77–7.67 (3H, m), 7.51–7.45 (3H, m), 7.11–7.09

(2H, m), 7.08 (1H, d, *J* 17.0 Hz), 6.95 (1H, d, *J* 8.2 Hz), 5.74 (1H, s), 3.91 (3H, s); δ_C (75.4 MHz, $CDCl_3$) 146.8, 145.8, 135.3, 133.8, 131.7, 131.4, 128.7, 127.8, 126.0, 125.8, 123.8, 123.6, 123.0, 120.6, 114.7, 108.6 and 56.0. HREIMS data: *m/z* $[M+H]^+$ for $C_{19}H_{17}O_2$, calculated=277.3440; observed=277.3441.

4.4.14. 3,4,4′-Trimethoxystilbene (Table 2/16b and 17b).[24f] White solid (mp 131–134 °C; lit.[24f] mp 133–135 °C); δ_H (300 MHz, $CDCl_3$) 7.38 (2H, d, *J* 8.5 Hz), 6.98–6.92 (2H, m), 6.86–6.76 (5H, m), 3.88 (3H, s), 3.83 (3H, s), 3.76 (3H, s); δ_C (75.4 MHz, $CDCl_3$) 159.1, 149.1, 148.6, 130.8, 130.3, 127.4, 126.4, 119.5, 114.1, 111.3, 108.6, 55.9, 55.8 and 55.3.

Acknowledgements

Two of us (V.K. and A.S.) are indebted to UGC and CSIR Delhi, respectively, for the award of SRF. The authors gratefully acknowledge the Director of I.H.B.T., Palampur for his kind cooperation and encouragement.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.034.

References and notes

1. (a) Medarde, M.; Clairac, R. P. L.; Ramos, A. C.; Caballero, E.; López, J. L.; Grávalos, D. G.; Feliciano, A. S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 229–232; (b) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. H. S.; Farnsworth, N. R.; Kinghorn, A. D.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218–220; (c) Dark, G. G.; Hill, S. A.; Prise, V. E.; Tozer, G. M.; Pettit, G. R.; Chaplin, D. J. *Cancer Res.* **1997**, *57*, 1829–1834; (d) Ohguchi, K.; Tanaka, T.; Kido, T.; Baba, K.; Iinuma, M.; Matsumoto, K.; Akao, Y.; Nozawa, Y. *Biochem. Biophys. Res. Commun.* **2003**, *307*, 861–863; (e) Lastra, C. A.; Villegas, I. *Mol. Nutr. Food Res.* **2005**, *49*, 405–430.
2. Iriti, M.; Faoro, F. *Med. Hypotheses* **2006**, *67*, 833–838.
3. (a) Marder, S. R.; Kippelen, B.; Jen, A. K. Y.; Peyghambarian, N. *Nature* **1997**, *388*, 845–851; (b) Grimsdale, A.; Holmes, A. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 402–428; (c) Meier, H.; Lehmann, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 643–645.
4. (a) Hegsted, D. M.; Ausman, L. M. *J. Nutr.* **1988**, *118*, 1184–1189; (b) Renaud, S.; De Lorgeril, M. *Lancet* **1992**, *339*, 1523–1526; (c) Pace-Asciak, C. R.; Hahn, S.; Diamandis, E. P.; Soleas, G.; Goldberg, D. M. *Clin. Chim. Acta* **1995**, *235*, 207–219; (d) Cheng, J.-C.; Fang, J.-G.; Chen, W.-F.; Zhou, B.; Yang, Li.; Liu, Z.-L. *Bioorg. Chem.* **2006**, *34*, 142–157.
5. (a) Bock, W. K. *Rev. Physiol. Biochem. Pharmacol.* **1994**, *125*, 1–42; (b) Savouret, J.-F.; Antenos, M.; Quesne, M.; Xu, J.; Milgrom, E.; Casper, R. F. *J. Biol. Chem.* **2001**, *276*, 3054–3059; (c) Poirot, M.; Medina, P. D.; Delarue, F.; Perie, J. J.; Klaebe, A.; Faye, J. C. *Bioorg. Med. Chem.* **2000**, *8*, 2007–2016.
6. (a) Hermann, L. S. *Diabete Metab.* **1979**, *5*, 233–245; (b) Jackson, R. A.; Hawa, M. I.; Japan, J. B.; Sim, B. M.; Silvo, D.; Featherbe, L.; Kurtz, D. *Diabetes* **1987**, *36*, 632–640; (c) Manickam, M.; Ramanathan, M.; Jahromi, M. A. F.; Chansouria, J. P. N.; Ray, A. B. *J. Nat. Prod.* **1997**, *60*, 609–610; (d) Pezet, R. *FEMS Microbiol. Lett.* **1998**, *167*, 203–208; (e) Rimando, A. M.; Cuendet, M.; Desmarchelier, C.; Mehta, R. G.; Pezzuto, J. M.; Duke, S. O. *J. Agric. Food Chem.* **2002**, *50*, 3453–3457.
7. (a) Hatanaka, T.; Fujita, K.; Ohsumi, K.; Nakagawa, R.; Fukuda, Y.; Nihei, Y.; Suga, Y.; Akiyama, Y.; Tsuji, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3371–3374; (b) Pettit, G. R.; Grealish, M. P.; Jung, M. K.; Hamel, E.; Pettit, R. K.; Chapuis, J. C.; Schmidt, J. M. *J. Med. Chem.* **2002**, *45*, 2534–2542; (c) Kim, S.; Ko, H.; Park, J. E.; Jung, S.; Lee, S. K.; Chun, Y.-J. *J. Med. Chem.* **2002**, *45*, 160–164; (d) Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R. *Tetrahedron* **2006**, *62*, 4214–4226; (e) Li, W.; Li, H.; Li, Y.; Hou, Z. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7609–7611.
8. (a) Dey, B. B.; Row, K. K. *J. Indian Chem. Soc.* **1925**, *1*, 277–287; (b) Gusten, H.; Salzwedel, M. *Tetrahedron* **1967**, *23*, 173–185; (c) Belucci, G.; Chiappe, C.; Moro, G. L. *Tetrahedron Lett.* **1996**, *37*, 4225–4228; (d) Myers, A. G.; Tanaka, D.; Mannion, M. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251; (e) Wang, J.-X.; Fu, Y.; Hu, Y. *Angew. Chem., Int. Ed.* **2003**, *41*, 2757–2760; (f) Cella, R.; Stefani, H. A. *Tetrahedron* **2006**, *62*, 5656–5662.
9. (a) Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrwnce, N. J.; McGown, A. T. *J. Org. Chem.* **2001**, *66*, 8135–8138; (b) Borrel, C.; Thoret, S.; Cachet, X.; Guénard, D.; Tillequin, F.; Koch, M.; Michel, S. *Bioorg. Med. Chem.* **2005**, *13*, 3853–3864.
10. Späth, E.; Kromp, K. *Chem. Ber.* **1941**, *74*, 189–192.
11. (a) Buckles, R. E.; Bremer, K. *Org. Synth. Coll.* **1963**, *Vol. IV*, 777–779; (b) Wood, C. S.; Mallory, F. B. *J. Org. Chem.* **1964**, *29*, 3373–3377; (c) Chandrasekhar, S.; Karri, P. *Tetrahedron Lett.* **2006**, *47*, 2249–2251; (d) Sevenard, D. V. *Tetrahedron Lett.* **2003**, *44*, 7119–7120; (e) Cserényi, S.; Felföldi, K.; Forgo, P.; Pálinkó, I. *J. Fluorine Chem.* **2006**, *127*, 850–853.
12. Solladié, G.; Jacopé, Y. P.; Maignan, J. *Tetrahedron* **2003**, *59*, 3315–3321.
13. (a) Sovish, R. C. *J. Org. Chem.* **1959**, *24*, 1345–1347; (b) Cohen, L. A.; Jones, W. M. *J. Am. Chem. Soc.* **1960**, *82*, 1907–1911.
14. (a) Buckles, R. E.; Wheeler, N. G. *Org. Synth. Coll.* **1963**, *Vol. IV*, 857; (b) Sadanandan, E. V.; Pillai, S. K.; Lakshmikantham, M. V.; Billimoria, A. D.; Culpepper, J. S.; Cava, M. P. *J. Org. Chem.* **1995**, *60*, 1800–1805; (c) Locatelli, G. A.; Savio, M.; Forti, L.; Shevelev, I.; Ramadan, N. K.; Stivala, L. A.; Vannini, V.; Ubscher, U. H.; Spadari, S.; Maga, G. *Biochem. J.* **2005**, *389*, 259–268.
15. (a) Sharma, A.; Joshi, B. P.; Sinha, A. K. *Chem. Lett.* **2003**, *32*, 1186–1187; (b) Pathania, V.; Sharma, A.; Sinha, A. K. *Helv. Chim. Acta* **2005**, *88*, 811–817; (c) Sharma, A.; Kumar, V.; Sinha, A. K. *Adv. Synth. Catal.* **2006**, *348*, 354–360; (d) Kumar, V.; Sharma, A.; Sinha, A. K. *Helv. Chim. Acta* **2006**, *89*, 483–495; (e) Sinha, A. K.; Sharma, A.; Swaroop, A.; Kumar, V. *Tetrahedron* **2007**, *63*, 1000–1007; (f) Kumar, V.; Sharma, A.; Sharma, A.; Sinha, A. K. *Tetrahedron* **2007**, *63*, 7640–7646.
16. (a) Sinha, A. K.; Joshi, B. P.; Sharma, A. U.S. Patent 6,989,467, 2006; *Chem. Abstr.* **2004**, *141*, 71343; (b) Sinha, A. K.; Sharma, A.; Joshi, B. P. *Tetrahedron* **2007**, *63*, 960–965.
17. Abbott, T. W.; Johnson, J. R.; Clarke, H. T.; Brethen, M. R. *Org. Synth. Coll.* **1941**, *Vol. I*, 440–442.

18. (a) Peng, Y.; Song, G. *Green Chem.* **2003**, *5*, 704–706; (b) Sentets, S.; Martinez, M. C. R. M.; Vendier, L.; Donnadieu, B.; Huc, V.; Lugan, N.; Lavigne, G. *J. Am. Chem. Soc.* **2005**, *127*, 14554–14555; (c) Pawełczyk, A.; Zaprutko, L.; Renner. *Eur. J. Med. Chem.* **2006**, *41*, 586–591.
19. Nezhad, A. K.; Mokhtari, B.; Rad, M. N. S. *Tetrahedron Lett.* **2003**, *44*, 7325–7328 and references cited therein.
20. (a) Neuvonen, K.; Neuvonen, H.; löp, F. F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3495–3498; (b) Zhu, D.; Rios, B. E.; Rozzell, J. D.; Hua, L. *Tetrahedron: Asymmetry* **2005**, *16*, 1541–1546.
21. (a) Sale, S.; Tunstall, R. G.; Ruparelia, K. C.; Potter, G. A.; Steward, W. P.; Gescher, A. J. *Int. J. Cancer* **2005**, *115*, 194–201.
22. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (b) Marquez, H.; Loupy, A.; Calderonc, O.; Pérez, E. R. *Tetrahedron* **2006**, *62*, 2616–2621.
23. Sinha A. K.; Kumar, V.; Sharma, A. U.S. patent, 2006 (pending).
24. (a) Sinsheimer, J. E.; Smith, R. V. *Biochem. J.* **1969**, *111*, 35–41; (b) Becker, H.-D. *J. Org. Chem.* **1969**, *34*, 1211–1215; (c) Ali, M. A.; Kondo, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 1130–1136; (d) Speicher, A.; Schoeneborn, R. *Phytochemistry* **1997**, *45*, 1615–1616; (e) Chhor, R. B.; Singh, K. A.; Nosse, B.; Tandon, V. K. *Synth. Commun.* **2003**, *33*, 2519–2530; (f) Botella, L.; Nájera, C. *Tetrahedron* **2004**, *60*, 5563–5570; (g) Ferré-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Eur. J. Org. Chem.* **2005**, 3319–3325.