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Combinatorial synthesis, reversed-phase and normal-phase high-performance liquid chromatography elution data and liquid chromatography/positive atmospheric pressure chemical ionization tandem mass spectra of methoxylated and glycosylated resveratrol analogues

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Analyses of methoxylated and glycosylated stilbenes remain scarce in the literature because of the commercial unavailability of these compounds. Here a library of 22 compounds was synthesized by combinatorial chemistry. Their elution profiles were compared on three different columns (C18, C8, and silica) with those of seven commercial resveratrol analogues and two viniferins. The spectra recorded by liquid chromatography/positive atmospheric pressure chemical ionization tandem mass spectrometry (LC-APCI(+)-MS/MS) are discussed and recommendations made for easier identification of new stilbenes. Copyright © 2007 John Wiley & Sons, Ltd.

Hydroxystilbenes are low molecular weight polyphenols (180–400 g/mol) found in a narrow range of plants.[1] Like flavanoids, they are formed via the phenylalanine/polymalonate pathway, but the last step is catalyzed by stilbene synthase instead of chalcone synthase.[2,3] Among them, *trans*-resveratrol (**2**.) shows anticarcinogenic, antiviral, antioxidant, anti-inflammatory, and estrogenic activities.[3,4] *trans*-Resveratrol (**2**.) has been mainly found in grapes (at concentrations ranging from 0.5–39 mg/kg[5,6]), peanuts and pistachios (at concentrations from 0.03–1.92 mg/kg[7,8] and 0.09–1.67 mg/kg,[8] respectively), cocoa (at levels close to 0.5 mg/kg),[9] and hop (at levels from 0.2–1.2 ppm).[10,11]

To a lesser extent than resveratrol, analogues such as piceid (**21**.), piceatannol (**3**.), and pterostilbene (**11**.) (see Fig. 1) exhibit similar activities.[1] The resveratrol glucoside *trans*-piceid (**21**.) has been quantified in grapes, rhubarb, peanut butter, cocoa, and hop.[9,11–20] A tetrahydroxystilbene, *trans*-piceatannol (**3**.), has been detected in grapes (10 mg/kg in table grapes), rhubarb, various species of *Vaccinium* (blueberries) and sugar cane,[16,20–27] whilst its glucoside *trans*-astringin (**23**.) has been found only in grape and rhubarb.[15–17,19,25] The dihydroxystilbene pinosylvin (**1**.) has been detected in pine kernel.[1] Grapes (35 ng/g) and *Vaccinium* spp. also show interesting levels of a dimethoxyhydroxystilbene, *trans*-pterostilbene[13,27] (**11**.). Rhaponticin (**26**.), a methoxytrihydroxystilbene glucoside, seems present only in rhubarb.[12] Because of the very low concentrations of stilbene analogues, specific techniques such as high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) are needed to identify and quantify them in plants. Unfortunately, most of them are commercially unavailable.

Combinatorial chemistry, a method initially developed by Geysen *et al*.,[28] has been recently applied in agrochemistry to characterize commercially unavailable flavors like thioesters and polyfunctional thiols.[29–35]

This 'one-pot' approach was used here for the first time to synthesize two libraries of stilbenes, one including 19 methoxylated stilbenes and the other, 3 glucosides. Both of them were analyzed on three HPLC columns with detection by ultraviolet (UV) and atmospheric pressure chemical ionization tandem mass spectrometry in positive mode (APCI(+)-MS/MS). The elution and MS data were further compared with those of seven commercial stilbenes and two viniferins (resveratrol dimers).

EXPERIMENTAL

Chemicals

trans-Resveratrol, *trans*-piceid, *trans*-piceatannol, *trans*-pterostilbene, rhaponticin, acetobromo-α,D-glucose, *N*-methyl-*N*-nitro-*p*-toluenesulfamide, formic acid, and potassium hydroxide were supplied by Sigma-Aldrich (Bornem, Belgium). *trans*-Astringin and *trans*-pinosylvin were obtained from Sequoia Research Products (Oxford, UK). Ethanol (97%) was purchased from Belgaco (Gent, Belgium) and absolute

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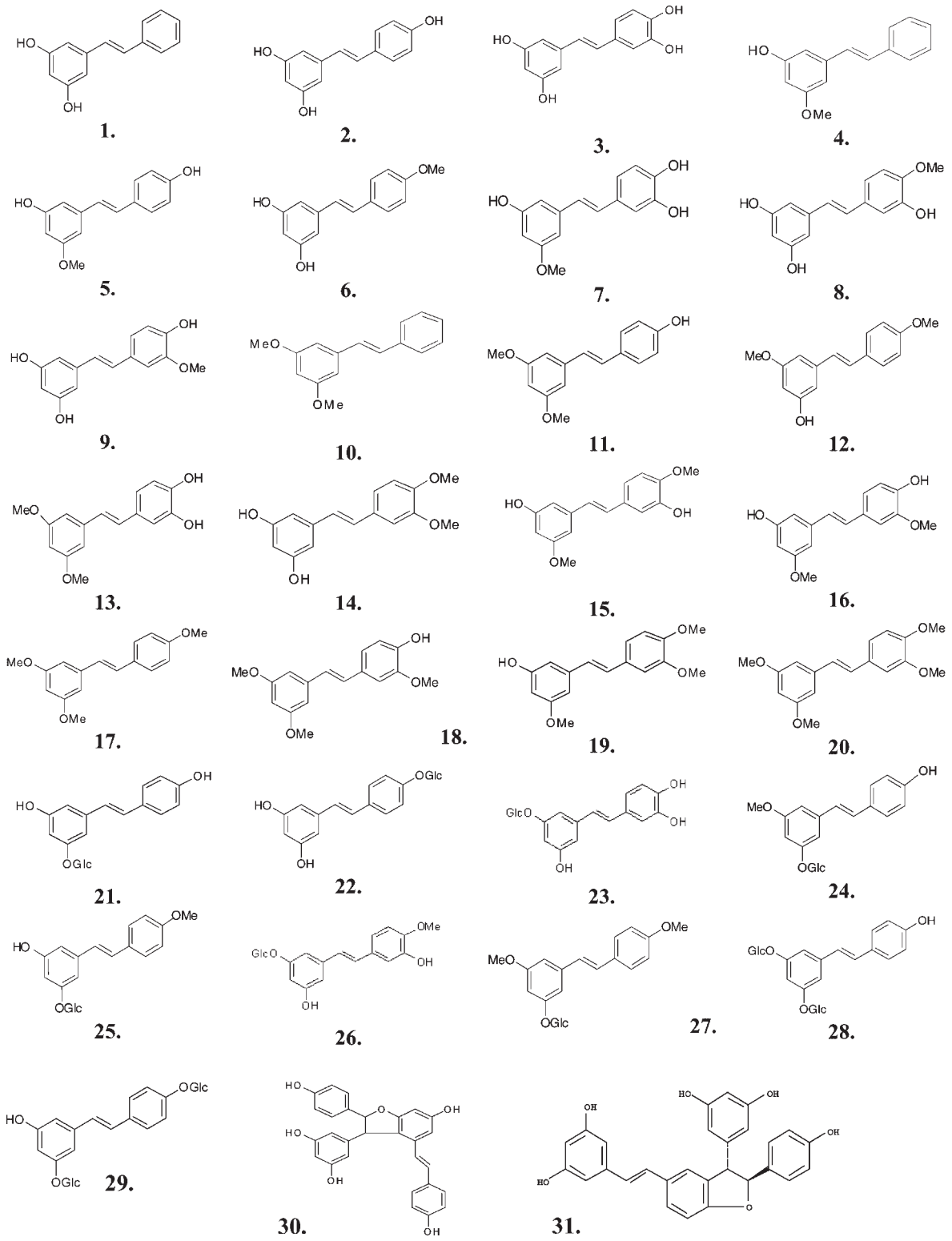

Figure 1. Structures of 9 commercial and 22 synthesized stilbenes.

ethanol from Fisher Scientific (UK). Methanol and dichloromethane were supplied by Romil (Cambridge, UK). Acetonitrile was obtained from Fisher Scientific (UK). Aqueous solutions were made with Milli-Q (Millipore, Bedford, MA, USA) water. δ-Viniferin and ε-viniferin standards were a kind gift from Dr X. Vitrac and Prof. J-M. Mérillon (Institut des Sciences de la Vigne et du Vin, Université Victor Segalen Bordeaux 2, France).

Combinatorial synthesis of methoxystilbenes

A library of methoxylated analogues of resveratrol, pinosylvine, piceid, and piceatannol was obtained according to a protocol inspired from Furniss *et al.*[36] Under red light, 5 mL of 97% ethanol was added to a solution of 1 g potassium hydroxide in 1.5 mL water. This solution was placed in a distillation flask equipped with a dropping funnel and a condenser. The distillation flask was heated in a water bath at

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60–65°C and a solution of 4.3 g *N*-methyl-*N*-nitro-*p*-toluenesulfamide in 25 mL diethyl ether was introduced dropwise into the flask for 45 min. The combined ethereal solution was added in small portions to the flask containing 250 mg of each stilbene (resveratrol, pinosylvine, piceid, and piceatannol) dissolved in 5 mL methanol (Fig. 2). Addition was stopped when the solution acquired a pale yellow color. The solvent was evaporated before analysis by HPLC/MS/MS.

Synthesis of stilbene glycosides

A library of glycosylated analogues of resveratrol was obtained according to Regev-Shoshani *et al.*[37] Under red light, 5 mg resveratrol, 9 mg acetobromo-α,D-glucose, and 2.45 mg potassium hydroxide were dissolved in 180 μL ethanol (Fig. 3). The mixture was stirred for 1 week at room temperature. Then 500 μL ethanol was added before HPLC analysis.

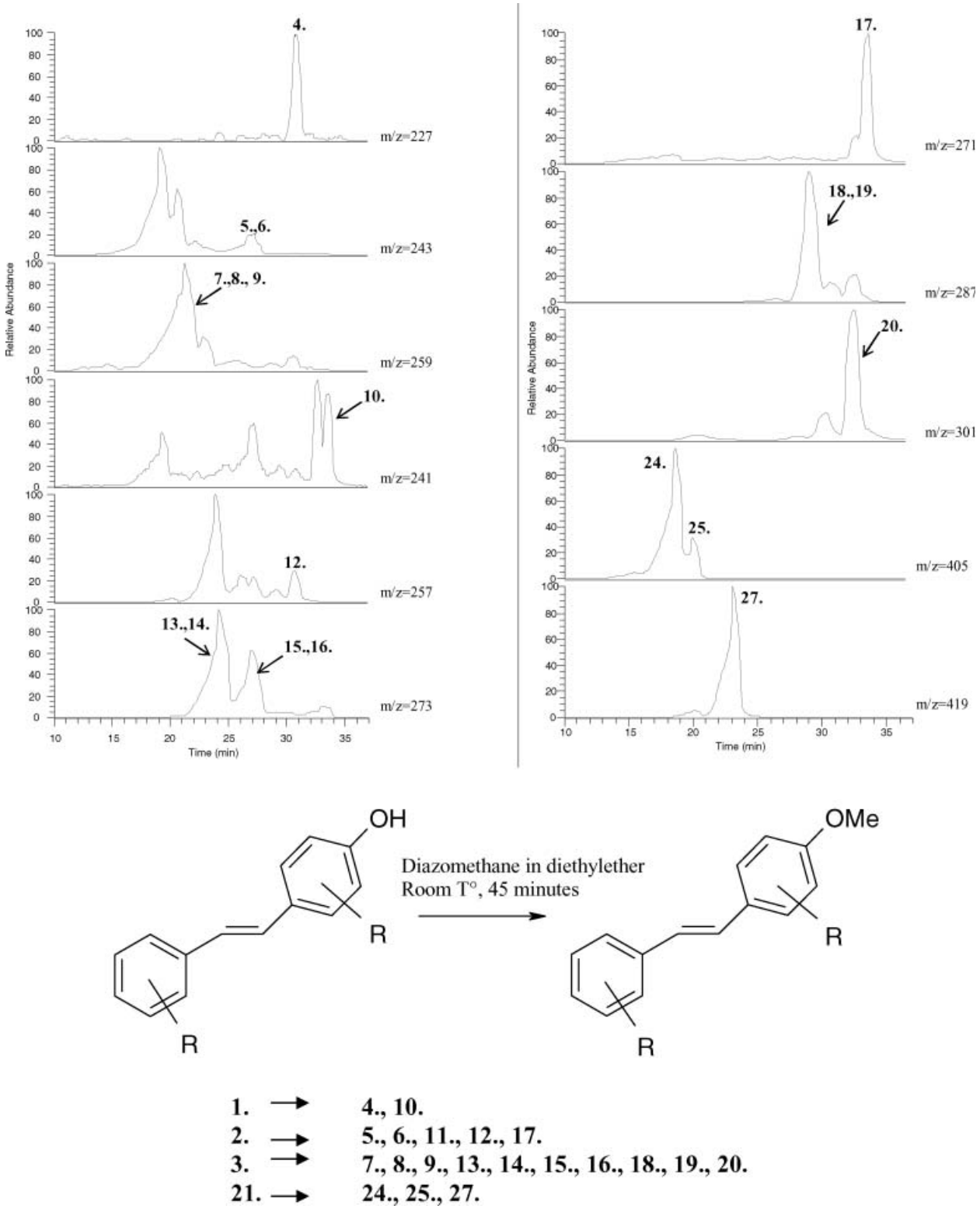

Figure 2. Synthesis scheme and RP-HPLC/MS/MS chromatograms (C18 column) of the library of methoxylated analogues of *trans*-pinosylvine (**1**.), *trans*-resveratrol (**2**.), *trans*-piceatannol (**3**.), and *trans*-piceid (**21**.).

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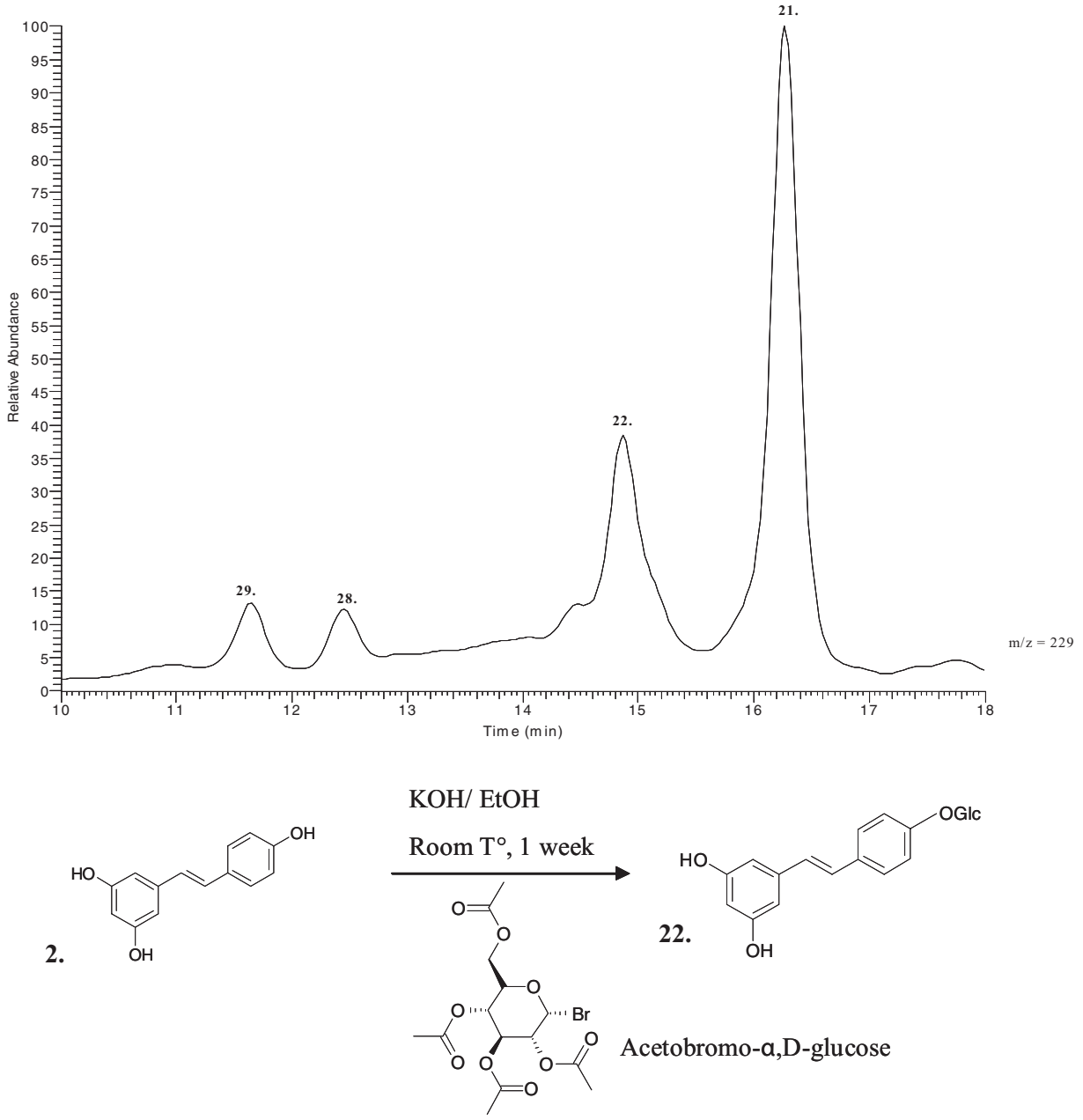

Figure 3. Synthesis scheme and RP-HPLC/MS/MS chromatograms (C18 column) of the glycosylated library issued from *trans*-resveratrol.

Reversed-phase (RP)-HPLC/MS/MS analysis of stilbenes

RP-HPLC analyses were performed on two different columns: a C18 Prevail column (150 × 2.1 mm, 2 μm) and a C8 column (150 × 2.1 mm, 2 μm), both from Alltech (Deerfield, IL, USA). Each was eluted with a linear gradient from water containing 1% acetonitrile and 0.1% formic acid (A) to acetonitrile (B). Gradient elution was as follows: from 95% A to 55% in 23 min, 55% to 0% in 7 min, and isocratic for 10 min at a flow rate of 200 μl/min. A volume of 10 μL of sample were injected into the column kept at 30°C. Analysis was carried out on a Finnigan Mat HPLC SpectraSystem equipped with a quaternary pump with degasser (model P4000), an autosampler (model AS3000) and a diode array detector (model UV6000LP). The system was controlled with the Xcalibur software version 1.2 (Finnigan Mat). Mass spectra were acquired using a LCQ mass spectrometer equipped with an APCI source (Finnigan Mat). The following APCI inlet conditions were applied in positive mode: vaporization temperature, 470°C; capillary voltage, 3V; capillary temperature, 175°C; sheath gas, 40 psi; auxiliary gas, 7 psi; discharge current 5 μA. After the first monitoring at $m/z = [M+H]^+$ (see Table 1), collision-induced dissociation (CID) spectra were recorded at 37% relative collision energy. For viniferins, an ESI source in negative mode was also tested. After the first monitoring at $m/z = 453$, CID spectra were recorded at 37%. The following conditions were applied: source voltage, 4.5 kV; capillary voltage, 36 V;

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Table 1. LC/APCI(+)-MS/Ms data of 9 commercial (C) and 22 synthesized (S) stilbenes. Retention times (min) and relative retentions to resveratrol (values in brackets) measured on three HPLC columns.[a] *m/z* = selected mass for MS/MS analysis

N°	Name	$m/z = [M+H]^+$	RT C18 (relative value)	RT C8 (relative value)	RT Silica (relative value)	N°	Name	$m/z = [M+H]^+$	RT C18 (relative value)	RT C8 (relative value)	RT Silica (relative value)
1.(C)	Pinosylvin or 3,5-dihydroxystilbene	213	28.2 (1.3)	24.6 (1.3)	4.3 (1.0)	**17**.(S)	3,4′,5-Trimethoxystilbene	271	33.5 (1.5)	30.3 (1.6)	3.9 (0.9)
2.(C)	Resveratrol or 3,4′,5-trihydroxystilbene	229	21.9 (1.0)	18.5 (1.0)	4.5 (1.0)	**18**.(S)	4′-Hydroxy-3,5,5′-methoxystilbene	287	29.7 (1.4)	26.9 (1.5)	3.9 (0.9)
3.(C)	Piceatannol or 3,3′,4′,5-tetrahydroxystilbene	245	18.7 (0.9)	15.7 (0.8)	5.5 (1.2)	**19**.(S)	3-Hydroxy-4′,5′,5-trimethoxystilbene	287	29.7 (1.4)	26.9 (1.5)	3.9 (0.9)
4.(S)	3-Hydroxy-5-methoxystilbene	227	30.9 (1.4)	28.4 (1.5)	3.8 (0.8)	**20**.(S)	3,4′,5,5′-Tetramethoxystilbene	301	32.6 (1.5)	29.7 (1.6)	3.9 (0.9)
5.(S)	3,4′-Dihydroxy-5-methoxystilbene	243	27.8 (1.3)	24.3 (1.3)	4.0 (0.9)	**21**.(C)	Piceid or 3,4′,5-trihydroxystilbene-3-*O*-β-D-glucopyranoside	391	16.4 (0.7)	14.0 (0.8)	8.4 (1.9)
6.(S)	3,5-Dihydroxy-4′-methoxystilbene	243	27.8 (1.3)	24.3 (1.3)	4.0 (0.9)	**22**.(S)	Resveratroloside	391	14.8 (0.7)	12.7 (0.7)	9.9 (2.2)
7.(S)	3,4′,5′-Trihydroxy-5-methoxystilbene	259	22.3 (1.0)	19.4 (1.0)	4.2 (0.9)	**23**.(C)	Astringin or 3,3′,4′,5-tetrahydroxystilbene-3-*O*-β-D-glucopyranoside	407	14.2 (0.6)	12.2 (0.7)	11.5 (2.6)
8.(S)	3,5,5′-Trihydroxy-4′-methoxystilbene	259	22.3 (1.0)	19.4 (1.0)	4.2 (0.9)	**24**.(S)	3,4′-Dihydroxy-5-methoxystilbene-3-O-β-D-glucopyranoside	405	19.9 (0.9)	17.8 (0.9)	8.0 (1.8)
9.(S)	3,4′,5-Trihydroxy-5′-methoxystilbene	259	22.3 (1.0)	19.4 (1.0)	4.2 (0.9)	**25**.(S)	3,5-Dihydroxy-4′-methoxystilbene-3-*O*-β-D-glucopyranoside	405	21.2 (0.9)	19.1 (1.0)	8.0 (1.8)
10.(S)	3,5-Dimethoxystilbene	241	33.4 (1.5)	30.6 (1.7)	3.8 (0.8)	**26**.(C)	Rhaponticin or 3,3′,5-trihydroxy-4′-methoxystilbene-3-*O*-β-D-glucopyranoside	421	17.5 (0.8)	15.0 (0.8)	7.4 (1.6)
11.(C)	Pterostilbene or 4′-hydroxy-3,5-dimethoxystilbene	257	30.9 (1.4)	28.2 (1.5)	3.9 (0.9)	**27**.(S)	3-Hydroxy-5,4′-dimethoxystilbene-3-*O*-β-D-glucopyranoside	419	24.6 (1.1)	22.1 (1.2)	9.9 (2.2)
12.(S)	5-Hydroxy-3,4′-dimethoxystilbene	257	31.0 (1.4)	28.3 (1.5)	3.9 (0.9)	**28**.(S)	3,4′,5-Trihydroxystilbene-3,5-O-β-D-diglucopyranoside	553	12.5 (0.6)	10.5 (0.6)	17.4 (3.9)
13.(S)	4′,5′-Dihydroxy-3,5-dimethoxystilbene	273	25.1 (1.2)	22.2 (1.2)	4.1 (0.9)	**29**.(S)	3,4′,5-Trihydroxystilbene-3,4′-O-β-D-diglucopyranoside	553	11.7 (0.5)	9.4 (0.5)	19.0 (4.2)
14.(S)	3,5-Dihydroxy-4′,5′-dimethoxystilbene	273	25.1 (1.1)	22.2 (1.2)	4.1 (0.9)	**30**.(C)	ε-Viniferin	455	24.0 (1.1)	21.0 (1.1)	3.8 (0.8)
15.(S)	3,5′-Dihydroxy-4′,5-dimethoxystilbene	273	27.9 (1.3)	24.3 (1.3)	4.1 (0.9)	**31**.(C)	δ-Viniferin	455	26.0 (1.2)	23.1 (1.2)	3.8 (0.8)
16.(S)	3,4′-Dihydroxy-5,5′-dimethoxystilbene	273	27.9 (1.3)	24.3 (1.3)	4.1 (0.9)						

[a] Elution in reversed phase with water containing 1% acetonitrile and 0.1% formic acid (A) and acetonitrile (B) from 95% A to 55% in 23 min, 55% to 0% in 7 min, and isocratic for 10 min at a flow rate of 200 μL/min. Elution in normal phase with dichloromethane (A) to methanol (B) from 85% A to 15% in 60 min, and isocratic for 15 min at a flow rate of 200 μL/min.

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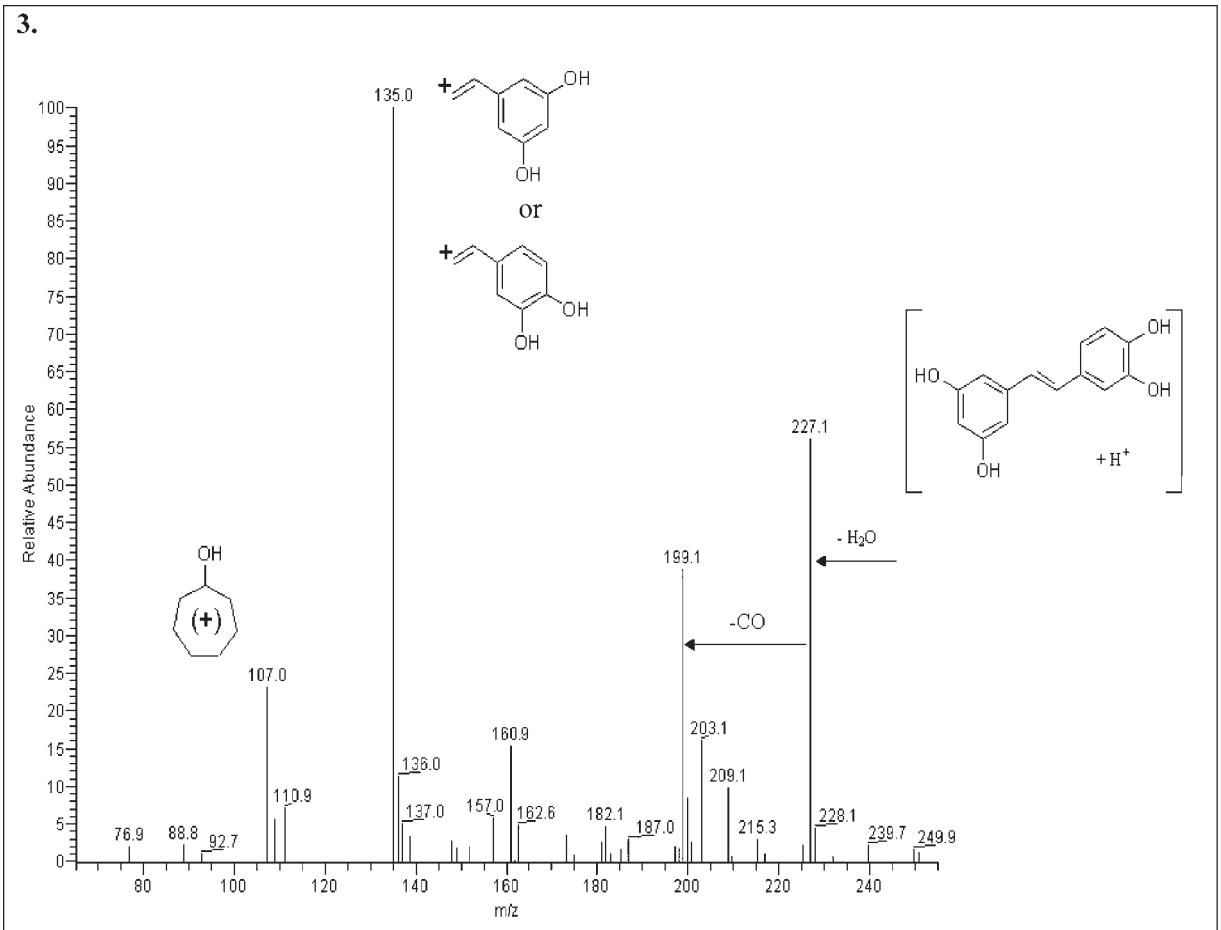


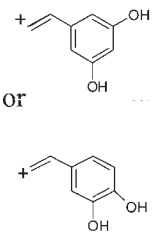
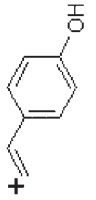
	[M +H-H_2O]$^+$	[M +H-H_2O-CO]$^+$			
1.	195 (30)	167 (5)	135 (100)		107 (12)
2.	211 (36)	183 (11)	135 (100)	119 (16)	107 (15)
3.	227 (55)	199 (38)	135 (100)		107 (24)

Figure 4. LC-APCI(+)-MS/MS spectra and hypothetical fragmentations of three hydroxystilbenes. Main product ions are given with relative intensity in parentheses (100 for the most abundant ion). $[M+H]^+$ was the first selected ion.

capillary temperature, 225°C; sheath gas, 70 psi; and auxiliary gas, 20 psi.

Normal-phase (NP)-HPLC/MS/MS analyses of stilbenes

Analyses were performed on an Alltima Silica column (250 × 2.1 mm, 2 μm) (Alltech, Deerfield, IL, USA) eluted with a linear gradient from dichloromethane to methanol. Gradient elution was as follows: from 85% dichloromethane to 15% in 60 min, and isocratic for 15 min at a flow rate of 200 μL/min. Volumes of 10 μL of sample were injected into the column kept at 30°C. The mass spectrometry conditions were the same as those described above.

RESULTS AND DISCUSSION

Combinatorial synthesis of methoxylated analogues

A library of methoxylated analogues was synthesized from pinosylvin (**1**.), resveratrol (**2**.), piceatannol (**3**.) and piceid (**21**.) (Fig. 2). As expected, monomethoxylated stilbenes

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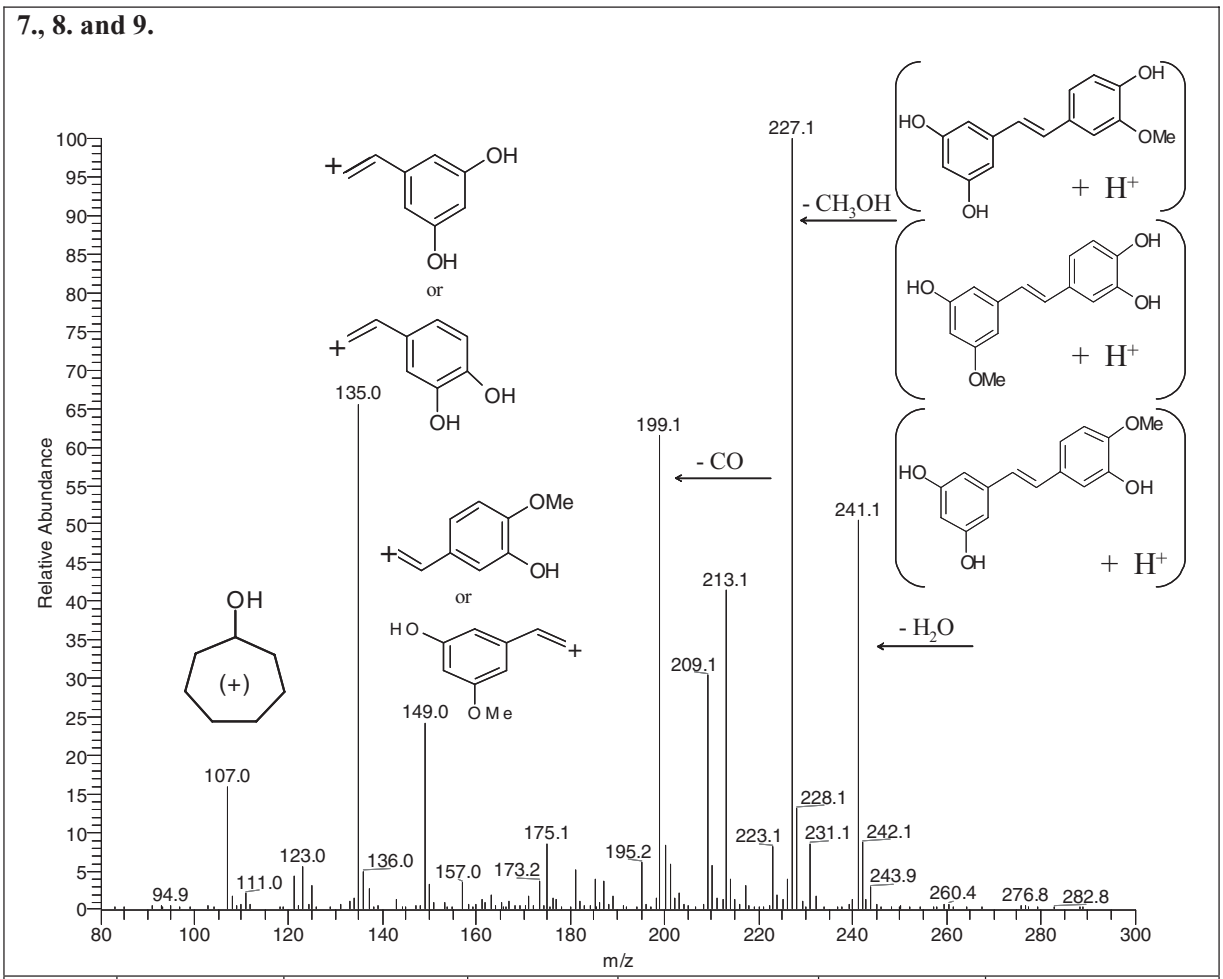


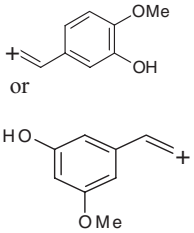
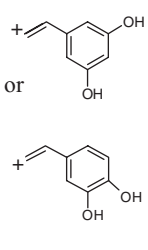
	$[M+H-H_2O]^+$	$[M+H-CH_3OH]^+$	$[M+H-H_2O-CO]^+$			
4.	209 (13)	195 (23)		149 (100)		
5., 6.	225 (37)	211 (68)	183 (21)	149 (86)	135 (100)	107 (25)
7., 8., 9.	241 (50)	227 (100)	199 (62)	149 (24)	135 (65)	107 (16)

Figure 5. LC/APCI(+)-MS/MS spectra and hypothetical fragmentations of six monomethoxystilbenes. Main product ions are given with relative intensity in parentheses (100 for the most abundant ion). $[M+H]^+$ was the first selected ion.

eluted from the reversed-phase columns (C18 and C8) after the starting reagent (e.g.: retention time **4.** > **1.**, **5./6.** > **2.**, **7.–9.** > **3.**) (see Table 1) but before their dimethoxylated (e.g.: **4.** < **10.**, **5./6.** < **11./12.**, **7.–9.** < **13.–15.**) and trimethoxylated analogues (e.g.: **11.–12.** < **17., 13.–15.** < **18./19.**). Not surprisingly, compounds eluted from the normal-phase silica column in the inverse order. In this case most retention times were too short for good resolution. Among our stilbenes, pterostilbene (**11.**) gave the shortest retention time (RT) (3.9 min) on the silica column and piceid (**21.**) the longest (8.4 min). All methoxylated analogues eluted before 8.0 min. Compounds **11./12.** co-eluted from the silica column, as did compounds **24./25.**, whereas these compounds were separated by the reversed-phase columns. None of the columns separated the very close monomethoxylated resveratrol isomers (**5.** and **6.**), monomethoxylated piceatannol analogues (**7.**, **8.**, **9.**), or di- and trimethoxylated piceatannol-derived isomers (**13.** and **14.**; **15.** and **16.**; **18.** and **19.**). MS/MS or selected ion monitoring (SIM) detection is therefore needed to quantify them separately.

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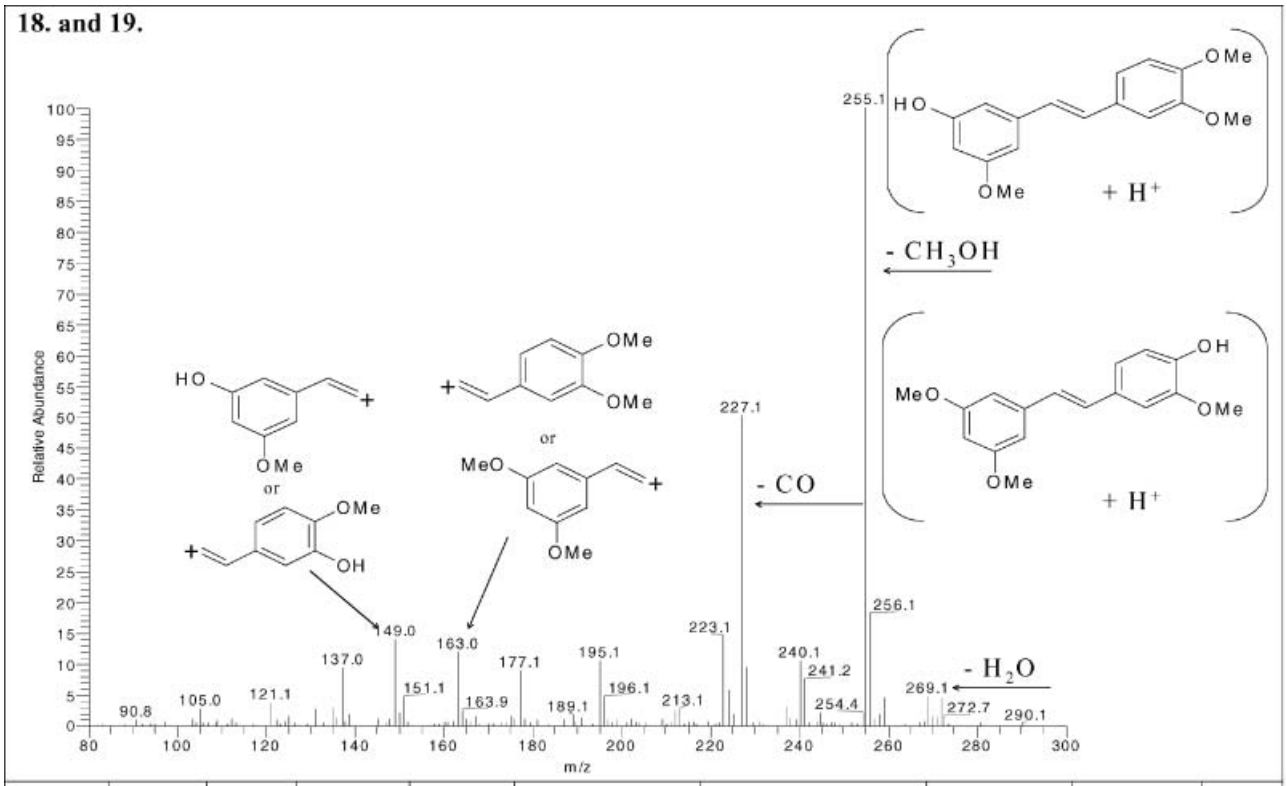


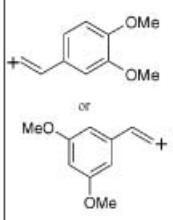
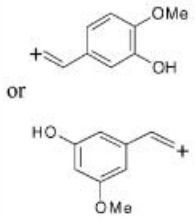
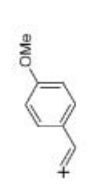
	$[M+H]^+$	$[M+H-H_2O]^+$	$[M+H-CH_3OH]^+$	$[M+H-CH_3OH-CO]^+$					other
10.		223 (18)	209 (81)	181 (53)					117 (100)
11.		239 (14)	225 (100)	197 (49)	163 (13)		133 (97)	119 (15)	145 (63)
12.		239 (14)	225 (83)	197 (24)		149 (100)			
13., 14.		255 (9)	241 (100)	213 (67)					
15., 16.		255 (39)	241 (100)	213 (53)		149 (92)			
17.			239 (100)	211 (25)					147 (80)
18., 19.		269 (5)	255 (100)	227 (51)	163 (13)	149 (14)			
20.	301 (100)								

Figure 6. LC/APCI(+)-MS/MS spectra and hypothetical fragmentations of eleven di-, tri- and tetramethoxystilbenes. Main product ions are given with relative intensity in parentheses (100 for the most abundant ion). $[M+H]^+$ was the first selected ion.

Combinatorial synthesis of resveratrol glycosides

A second library of glycosylated analogues was synthesized from resveratrol (Fig. 3). From the reversed-phase columns, the diglucosylated stilbenes eluted before the monoglucosylated analogues and the starting reagent (**29./28.** < **22./21.** < **2.**). Again the inverse order of elution was observed with the silica phase. All columns effectively separated all compounds.

LC/APCI(+)-MS/MS spectra of methoxylated stilbenes

All hydroxystilbenes yielded cations having lost a water molecule (Fig. 4) and all monomethoxylated stilbenes yielded cations having lost a methanol molecule (Fig. 5). In most cases, however, the cation issued from the loss of a phenyl ring (135 in **1.**, **2.**, **3.**, **6.**, **7.**, **8.**, **9.** and 149 in **4.**, **5.**, **7.**, **8.**, **9.**) was favored. For di-, tri- and tetramethoxylated

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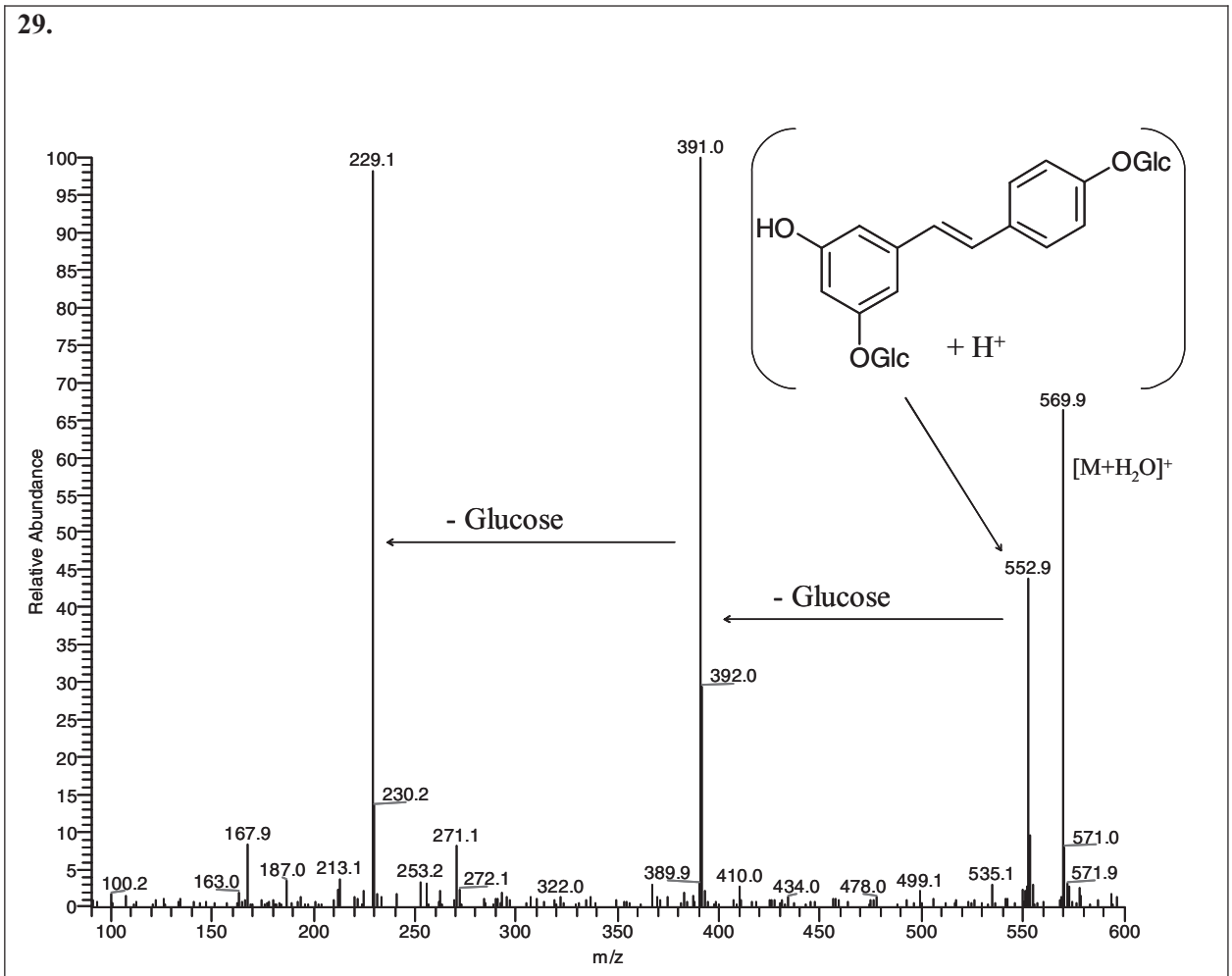

	$[M+H_2O]^+$	$[M+H]^+$	$[M+H\text{-glucose}]^+$	$[M+H-2\ glucoses]^+$	$[M+H-H_2O]^+$	$[M+H-2\ H_2O]^+$
21.			229 (100)		373 (27)	355 (33)
22.			229 (100)			
23.			245 (100)		389 (35)	371 (34)
24.			243 (100)		387 (5)	369 (14)
25.			243 (100)		387 (23)	369 (30)
26.			259 (100)		403 (19)	385 (23)
27.			257 (100)			
28.	570 (100)	553 (7)	391 (23)	229 (38)		
29.	570 (67)	553 (44)	391 (100)	229 (99)		

Figure 7. LC/APCI(+)-MS/MS spectra and hypothetical fragmentations of nine stilbene mono- and diglucosides. Main product ions are given with relative intensity in parentheses (100 for the most abundant ion). $[M+H]^+$ was the first selected ion.

compounds (Fig. 6), loss of a methanol molecule was again observed, except in the case of **20**., which did not fragment at all. Other spectra could probably be obtained by increasing the relative collision energy. Mass spectrometry failed to distinguish two pairs of coeluting compounds: **13**. and **14**. on the one hand, **18**. and **19**. on the other.

LC/APCI(+)-MS/MS spectra of resveratrol glucosides

As depicted in Fig. 7, fragmentation of the monoglucosides was characterized by the loss of the sugar, leading in all cases to an intense aglycone $[M+H\text{-glucose}]^+$ ion. In the case of diglucosylated compounds (Fig. 7), the successive losses of both sugars were observed (e.g: **28**. vs. **21**.). Surprisingly, **28**. and **29**. both displayed a strong $[M+H_2O]^+$ ion.

MS/MS spectra of resveratrol dimers

As expected, both viniferins eluted after resveratrol from the reversed-phase columns and before resveratrol from the silica normal-phase column (Table 1). The latter, however, did not effectively separate ε-viniferin (**30**.) from δ-viniferin (**31**.). The LC/APCI(+)-MS/MS spectra of these compounds

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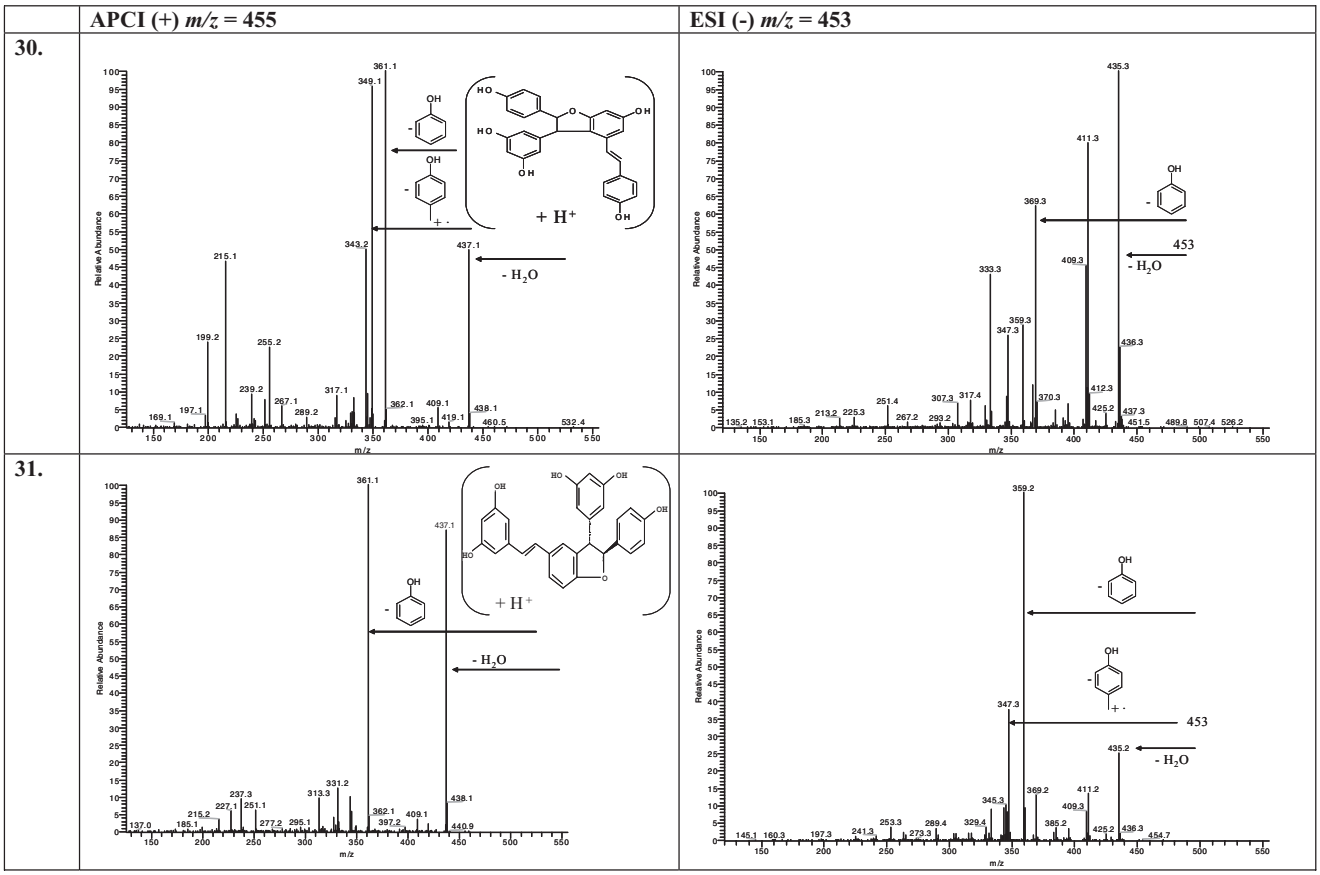

Figure 8. LC/APCI(+)-MS/MS and LC/ESI(-)-MS/MS spectra of ε- (**30**.) and δ-viniferins (**31**.) with hypothetical fragmentations.

at $m/z = 455$ are given on the left of Fig. 8. As previously mentioned in the literature,[38,39] $m/z = 437$ ($[M+H-H_2O]^+$) and 361 ($[M+H-94]^+$, loss of a phenolic group) characterized both dimers. On the other hand, m/z 349 ($[M+H-106]^+$) was specific to ε-viniferin (**30**.). On the right of Fig. 8 are given the MS/MS spectra obtained in LC/ESI(−)-MS/MS mode. For such heavy compounds, this mode is recognized as more sensitive (a five-times-higher signal intensity in our case).

CONCLUSIONS

In conclusion, we have characterized 22 new stilbenes by taking advantage of two complementary and routine techniques, combinatorial chemistry and HPLC/MS/MS. Our data should help scientists to detect and quantify these compounds in complex natural media.

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