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ARTICLE

Improved Synthesis of Bioactive Stilbene Derivatives Applying Design of Experiments to the Heck-Matsuda Reaction

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Design of experiments was employed to optimize the reaction conditions used to synthesize stilbene derivatives. New Heck conditions were tested using several styrenes and aryldiazonium tetrafluoroborates, generating the desired stilbenes in good yields in all cases under very practical, economical and effective conditions. This methodology was used for the synthesis of bioactive stilbenes such as resveratrol, DMU-212, and their analogues.

Introduction

Resveratrol and its derivatives (Figure 1) have attracted considerable attention from the scientific community due to their numerous human health benefits, including chemoprevention and antitumor activity.[1] Resveratrol is a secondary metabolite produced in response to stress caused by fungi and bacteria. Therefore, it is a representative example of molecules that promote a natural plant defence called phytoalexin ("protector of plants").[2] In addition to their important role in plant defence, they can also promote beneficial effects to human health including both chemoprevention and antitumor activities, anti-inflammatory, antioxidant, antiproliferative, pro-apoptotic, cardioprotective, and antiviral properties.[3,4] Thus, this polyphenol has been studied for the treatment of atherosclerosis, heart disease, arthritis, autoimmune diseases, and cancer.[1]

To find new potential drug candidates, several analogues of polyoxygenated stilbenes, particularly resveratrol (**1**), have been synthesized and evaluated; some of these derivatives demonstrate improved activity over the natural product.[5] Many of these analogues also show improved pharmacokinetic properties compared to resveratrol. Examples of these bioactive analogues are shown in Figure 1.[5b,c,1]

Due to the scarcity of stilbene derivatives available in nature, different synthetic methodologies have been developed to meet the demand for compounds with better pharmacological properties. The 1,2-disubstituted double bond present in the stilbene unit is a key structural element and is usually constructed using Wittig or Horner-Wadsworth-Emmons reactions employing substituted benzaldehydes.[6] With the advent of the metal-catalyzed reactions, various methods have been developed for the preparation of these systems, resulting in better yields and stereocontrol: the Heck,[7] Suzuki,[8] Stille[9] and Negishi couplings,[10] olefin metathesis,[11] and the McMurry coupling between aldehydes and ketones.[12]

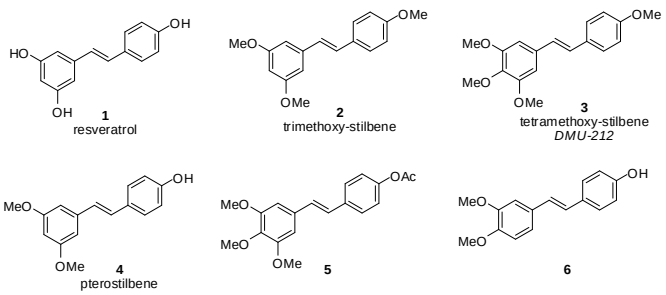

Figure 1: Example of some bioactive polyoxygenated stilbenes.

In 2008, we completed the synthesis of resveratrol **1**, trimethoxy-stilbene **2**, DMU-212 **3**, pterostilbene **4**, stilbene **5** and other stilbene derivatives using Heck arylation with aryldiazonium salts as the key step.[13] This method was highly effective at providing the Heck adduct in high yields and stereoselectivity when employing benzonitrile as the solvent. Most likely, benzonitrile acted as a Pd-complexing solvent, stabilizing the otherwise ligandless palladium intermediate. Although this solvent is safe in an organic laboratory,[14] its use would limit scaled-up processes due to its high boiling point and higher cost compared to other solvents. Therefore, the main objective of the present study was to utilize design of experiments (DOE)[15] to optimize the Heck-Matsuda reaction used to obtain key stilbene derivatives in high yields and selectivities while minimizing the use of benzonitrile as the solvent or co-solvent.

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Results and Discussion

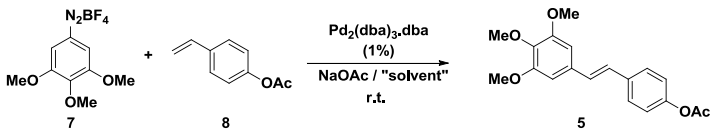
We began our investigation by applying an univariated method to optimize some preliminary analyses concerning the effect of the solvents on the arylation (Table 1). After analyzing the results in Table 1, the best yields were obtained for solvent systems containing benzonitrile as the solvent or co-solvent. To some extent, these results corroborate the previous work conducted in our laboratory (entry 1, Table 1).[13] Gratifyingly, excellent results were also obtained when using THF/PhCN and dioxane/PhCN as solvent systems (entries 2 and 3, Table 1), encouraging further optimization of this reaction.

Therefore, we tried to determine the optimal conditions for the Heck-Matsuda reaction using DOE. We focused on three experimental factors (temperature, solvent and catalyst loading).

A two-level full factorial and a centre point design are presented in Table 2. Eight experiments and three replicate centre points were used to develop the experimental design. The overall design of these experiments and their respective yields are shown in Table 3. The three centre-point experiments had an average yield of 86.6 % with a standard deviation of 4.3 %. The results were analyzed using Minitab software.[16]

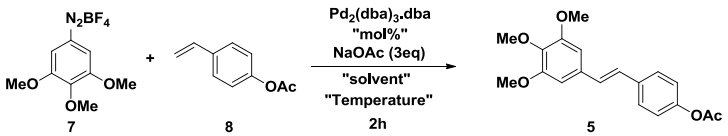
The maximum temperature used in the design was the boiling point of tetrahydrofuran (66 ºC), while the other two levels regarding the catalyst loading (1 mol% to 2 mol%) and solvent (pure THF to pure benzonitrile) were rationalized based on our preliminary results (Table 1 and ref. 13).

Table 1. Effect of the solvent on the Heck-Matsuda arylation.



Entry	Solvent	Time	Yield (%)
1	PhCN	2 h	88
2	THF/PhCN (3:1)	5 h	93
3	dioxane/PhCN (3:1)	6.5 h	87
4	THF	Overnight	55
5	H_2O/THF (3:1)	Overnight	11
6	pivalonitrile/PhCN (3:1)	Overnight	4

Table 2: Levels of the three factors in the factorial design.



Factor	Level (–)	Level (+)
Temperature (ºC)	30	66
[Cat] mol%	1.0	2.0
Solvent	THF	PhCN

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Table 3: Experiment 2^3 of factorial design.

Run	T	[Catalyst]	Solvent	Yield (%)
1	+	+	+	48
2	–	+	+	94
3	+	–	+	12
4	–	–	+	7
5	+	+	–	99
6	–	+	–	43
7	+	–	–	71
8	–	–	–	25

In Table 3, entry 5 displays an excellent result regarding the reaction yield (99%) in pure THF using 2 mol % of the catalyst $Pd_2(dba)_3$. This outcome was particularly important because it indicated that benzonitrile could be completely removed without negatively affecting the reaction. Figure 2 displays the standardized factor effects on the reaction performance. This figure shows the pronounced effect of increasing the catalyst concentration on the reaction yield compared to the standard deviation (Part B in Figure 2, standard deviation 4.3%). In addition, the effect of increasing the temperature while changing the solvent also improves the reaction efficiency (Part AC in Figure 2). Other factors, such as the solvent (C) and temperature (A), as well as combinations of catalyst loading and solvent (BC), temperature and solvent (AC), and all three (temperature, amount of catalyst and solvent, ABC), did not improve the reaction significantly; the feature values observed were below the standard deviation (Figure 2).

Relevant experimental information was also obtained using a contour plot of the catalyst concentration versus the temperature as a function of using either benzonitrile or tetrahydrofuran as the solvent (Figure 3). The best reaction yield was obtained when using tetrahydrofuran as solvent while increasing the temperature, whereas a decrease in the temperature provided the best reaction yield with benzonitrile (Figure 4).

Tetrahydrofuran was selected due to its low cost and lower boiling point compared to benzonitrile, making the Heck-Matsuda arylation a more practical and less costly procedure. Therefore, the best conditions for the experiments were those described in entry 5 (Table 3): THF with 2 mol% of palladium catalyst at 66 °C. Once the best conditions for producing stilbene derivative **5** were selected, they were also applied to the synthesis of other derivatives of different styrenes (Table 4).

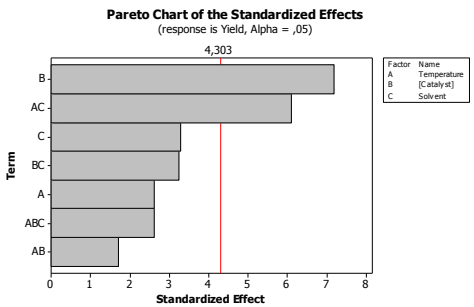

Figure 2: Standardized effects between the factors.

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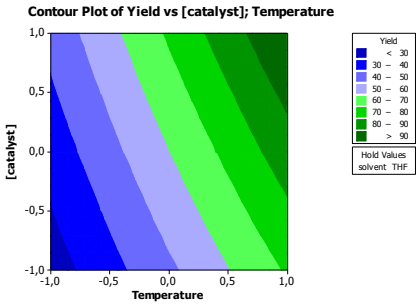


Figure 3: Contours plots of the yield versus the catalyst versus the temperature as a function of tetrahydrofuran as solvent.

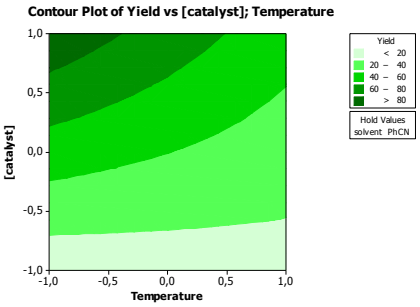
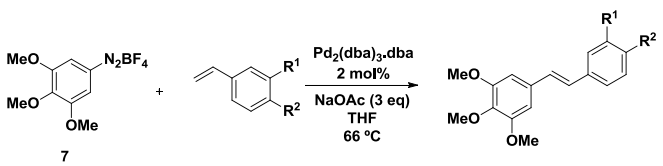


Figure 4: Contours plots of the yield versus the catalyst versus the temperature as a function of benzonitrile as solvent.

Table 4: Evaluation of the reaction scope under the selected conditions.



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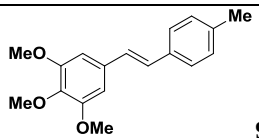
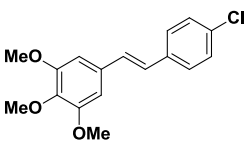
Entry	Product	Time (h)	Yield (%)
1	 9	2	80[b]
2	 10	3	76[b]

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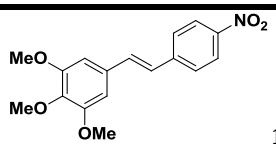
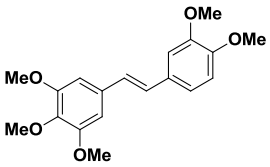
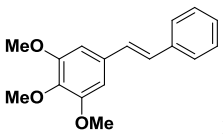
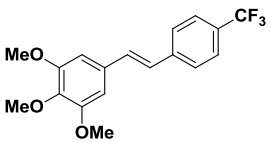
3	 **11**	4	87[a] (77)[b]
4	 **12**	2	83[a] (66)[b]
5	 **13**	2	91[b]
6	 **14**	4	78[a] (73%)[b]

[a] Yield determined by ^{1}H NMR.

[b] Isolated yield

These results clearly demonstrate the reproducibility and applicability of the design of experiments method, which led to excellent yields in all cases. Another important advantage of this method is that it enables the synthesis of stilbene derivatives with biological activities, such as DMU-212 **3**, resveratrol **1** and stilbene **6**, under more practical and scalable conditions (Scheme 1). Using this premise, intermediates **16** and **18** were obtained in 85% and 93% yields, respectively, as described in Scheme 1. These intermediates were converted into resveratrol **1** and derivative **6**, as previously reported.[13] Compound **3** (DMU-212) was obtained using the same method, with a good yield of 68% (Scheme 1). The synthesis of stilbenes **5**, **16** and **18** was also tested with a 10-fold increase in reaction scale, resulting in similar yields (0.9 g: 98%, 1.08 g: 81% and 1.19 g: 89%, respectively).

2-Methyltetrahydrofuran (Me-THF) was also evaluated as an appropriate reaction solvent because its Lewis base properties are similar to those of THF, and because of its increased use in industry as a less hazardous solvent facilitating product purification.[18] Three Heck-Matsuda reactions were tested using Me-THF (Table 5) employing our optimized conditions (2 mol% of palladium catalyst at 66 °C). The use of Me-THF allowed the synthesis of stilbene **16** in 89% yield. However, we observed a slight decrease in yields for stilbenes **18** and **5** when compared to the use of THF (75% and 61%, respectively). It is worth mentioning that these lower yields are probably related to the limited solubility of the diazonium salts in Me-THF.

Conclusion

In conclusion, we report here the use of the design of experiments method (DOE) for optimizing the synthesis of several stilbene derivatives, including resveratrol and DMU-212, two biologically active compounds using benign conditions. The method developed using DOE proved broad in scope as it allowed the evaluation of 8 styrenes and 3 aryldiazonium salts and proved especially useful for the synthesis of stilbenes **5**, **16** and **18** on gram scale for biological screenings. The DOE was instrumental for the replacement of benzonitrile as reaction solvent for THF or Me-THF, which are easily removed from the final products, making the overall process more practical and economical. The applicability of design of experiments to other Heck-Matsuda reactions is ongoing in our laboratory.

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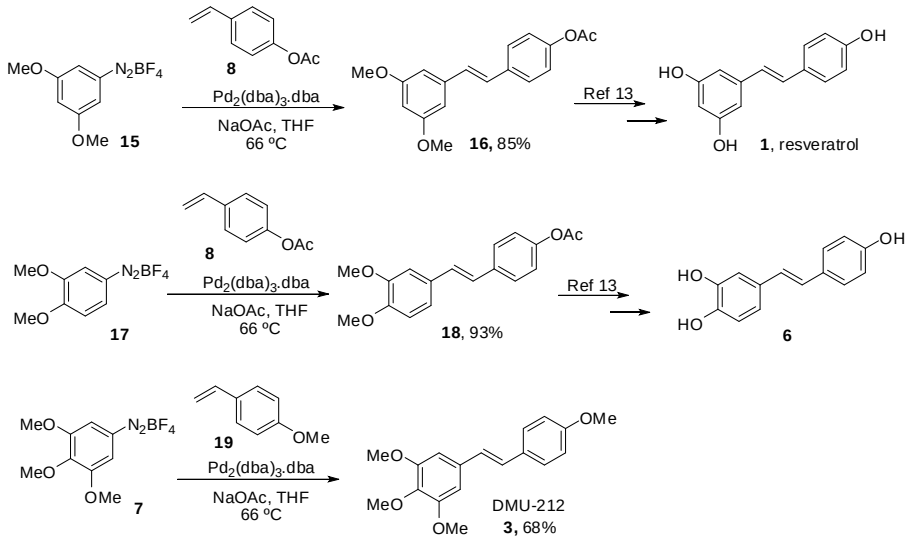
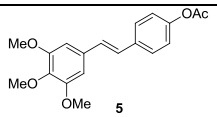
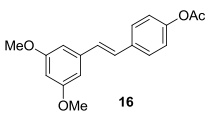
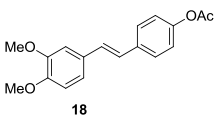


Scheme 1: Synthesis of resveratrol **1**, stilbene derivative **6** and DMU-212 (**3)**

Table 5: Evaluation of the Heck reaction using Me-THF as solvent.

Product	Yield, THF (%)	Yield, Me-THF (%)
 5	99.6	61
 16	85	89
 18	93	75

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Experimental section

$Pd_2(dba)_3$.dba was prepared as described in reference 17. Purification of the compounds reported in this study was performed using flash column chromatography using silica gel (230 to 400 mesh) as stationary phase, and the mobile phase is specified for each compound. For monitoring the reaction progress it was used thin-layer chromatography (TLC) on silica gel 60 and GF (5−40 μm thickness). TLC plates were either placed under UV light or stained with phosphomolybdic acid, followed by heating. ^{1}H and proton-decoupled ^{13}C NMR spectra were taken in $CDCl_3$ at 250 MHz (^{1}H) and 62.9 MHz (^{13}C); 400 MHz (^{1}H) and 100 MHz (^{13}C); or 500 MHz (1H) and 125 MHz (^{13}C). Data are reported as follows: chemical shift in ppm (δ), multiplicity, number of hydrogens, and coupling constants in Hertz (*J*). The multiplicity of the signals in the ^{1}H NMR spectra is described according to the convention: s = singlet, d = doublet, m = multiplet (multiplet).

General procedure for the Heck-Matsuda reaction: To a 10-mL tube equipped with a magnetic stirring bar were added $Pd_2(dba)_3$.dba,[17] sodium acetate (81 mg, 0.9 mmol) and the solvent (2 mL). The reaction mixture was brought to the desired temperature, followed by addition of the appropriate styrene (0.3 mmol), and the arenediazonium salt (103 mg, 0.36 mmol). The reaction progress was monitored by the evolution of dinitrogen. When completed, the reaction mixture was filtered through a plug of silica gel using ethyl acetate and concentrated under reduced pressure. The crude reaction was then purified by column chromatography using hexane:ethyl acetate as eluent.

(*E*)-1,2,3-trimethoxy-5-(4-methoxystyryl)benzene 3 (DMU-212): ^{1}H NMR: $CDCl_3$, 400 MHz, δ (ppm): δ 3.83 (s, 3H); 3.87 (s, 3H); 3.92 (s, 6H); 6.72 (s, 2H); 6.88-6.99 (m, 4H); 7.45 (d, J = 9.0 Hz, 2H). The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[13]

(*E*)-4-(3,4,5-trimethoxystyryl)phenyl acetate 5: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): δ 2.29 (s, 3H); 3.87 (s, 3H); 3.90 (s, 6H); 6.72 (s, 2H); 6.97 (s, 2H); 7.09 (d, *J* = 8.5 Hz, 2H); 7.50 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (62.5 MHz, CDCl3) δ 21.1; 56.1; 61.0; 103.6; 121.8; 127.1; 127.3; 128.9; 132.9; 135.0; 138.0; 150.0; 153.4; 169.5. The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[13]

(*E*)-1,2,3-trimethoxy-5-(4-methylstyryl)benzene 9: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): δ 2.37 (s, 3H); 3.88 (s, 3H); 3.93 (s, 6H); 6.74 (s, 2H); 6.97 (s, 2H); 7.18 (d, *J* = 8.0 Hz, 2H); 7.42 (d, *J* = 8.2 Hz, 2H). The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[19]

(*E*)-5-(4-chlorostyryl)-1,2,3-trimethoxybenzene 10: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): δ 3.87 (s, 3H); 3.91 (s, 6H); 6.72 (s, 2H); 6.93 (d, J = 16.4 Hz, 1H); 7.01 (d, *J* = 16.4 Hz, 1H); 7.31 (d, *J* = 8.5 Hz, 2H); 7.42 (d, *J* = 8.5 Hz, 2H). The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[20]

(*E*)-1,2,3-trimethoxy-5-(4-nitrostyryl)benzene 11: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): δ 3.89 (s, 3H); 3.93 (s, 6H); 6.78 (s, 2H); 7.04 (d, *J* = 16.1 Hz, 1H); 7.20 (d, *J* = 16.1 Hz, 1H); 7.63 (d, *J* = 8.8 Hz, 2H); 8.22 (d, *J* = 8.8 Hz, 2H). The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[21]

(*E*)-5-(3,4-dimethoxystyryl)-1,2,3-trimethoxybenzene 12: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): δ 3.87 (s, 3H); 3.91 (s, 3H); 3.92 (s, 6H); 3.95 (s, 3H); 6.73 (s, 2 H); 6.91 (m, 3H); 7.07 (m, 2H). The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[22]

(*E*)-1,2,3-trimethoxy-5-styrylbenzene 13: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): δ 3.87 (s, 3H); 3.91 (s, 6H); 6.74 (s, 2H); 7.02 (s, 2H); 7.30 (m, 3H); 7.50 (d, J = 7.30 Hz, 2H). The spectroscopic data obtained for this compound were consistent with the data reported in the literature.[23]

(*E*)-1,2,3-trimethoxy-5-(4-trifluoromethyl)styryl)benzene 14: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): δ 3.88 (s, 3H); 3.93 (s, 6H); 6.76 (s, 2H); 7.02 (d, *J* = 16.7 Hz, 1H); 7.13 (d, *J* = 16.7 Hz, 1H); 7.60 (s, 4H). The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[24]

(*E*)-4-(3,5-dimethoxystyryl)phenyl acetate 16: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): 2.31 (s, 3H); 3.83 (s, 6H); 6.40 (t, *J* = 2.25 Hz, 1H); 6.66 (d, *J* = 2.25 Hz, 2H); 6.98 (d, *J* = 16.5 Hz, 1H); 7.05-7.09 (m, 3H); 7.51 (d, *J* = 8.50 Hz, 2H). The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[13]

(*E*)-4-(3,4-dimethoxystyryl)phenyl acetate 18: ^{1}H NMR: $CDCl_3$, 250 MHz, δ (ppm): 2.31 (s, 3H); 3.90 (s, 3H); 3.95 (s, 3H); 6.86 (d, *J* = 8.5 Hz, 1H); 6.97 (d, *J* = 3.75 Hz, 2H); 7.02-7.09 (m, 4H); 7.49 (d, *J* = 8.5 Hz, 2H). The spectroscopic data obtained for this compound were fully consistent with the data reported in the literature.[13]

Acknowledgements

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Notes and references

[a] Chemistry Institute, State University of Campinas, UNICAMP, C.P. 6154, CEP 13084-971, Campinas, São Paulo, Brazil.

Electronic Supplementary Information (ESI) available: spectra for compounds **3**, **5**, **9**-**14**, **16** and **18**. See DOI: 10.1039/b000000x/

1. S. Fulda, *Drug Discov. Today* 2010, **15**, 757.
2. D.P. Hayes, *Med. Hypotheses* 2011, **77**, 765
3. N. Namasivayam; N.Y. *Ann. Acad. Sci.* 2011, **1215**, 60.
4. (a) J. Gusma; H. Malonne,; G. Atassi, *Carcinogenesis* 2001, **22**, 1111. (b) S. Pervaiz; A.L. Holme *Antioxid. Redox Signaling* 2009, **11**, 2851. (c) J.J. Docherty; T.J. Sweet; E. Bailey; S.A. Faith; T. Booth *Antiviral Res.* 2006, **72**, 171. (d) S.A. Faith; T.J. Sweet; E. Bailey; T. Booth; J. Docherty *J. Antiviral Res.* 2006, **72**, 242. (e) P. Saiko; A. Szkamry; W. Jaeger; T. Szekeres *Mutat. Res.* 2008, **658**, 68. (f) S. Bradamante; L. Barenghi; A. Villa *Cardiovasc. Drug Rev.* 2004, **22**, 169. (g) B.B. Aggerwal; A.

New Journal of Chemistry Accepted Manuscript

Bhardwaj; R.S. Aggarwal; N.P. Seeram; S. Shishodia; Y. Takada *Anticancer Res.* 2004, **24**, 2783. (h) C. Simon; R.G. Britton; H. Cai; A.J. Gescher, P.R. Jenkins; K. Brown *Tetrahedron Lett.* 2013, **69**, 6203.

5. (a) S.K. Lee; K.A. Nam; Y.H. Hoe; H-Y. Min; E-Y. Kim; H. Ko; S. Song; T. Lee; S. Kim *Arch. Pharm. Res.* 2003, **26**, 253. (b) L. Chen; Y. Zhang; X. Sun; H. Li; G. LeSage; A. Javer; X. Zhang; X. Wei; Y. Jiang; D. Yin *Bioorg. Med. Chem.* 2009, **17**, 4378. (c) B.W. Moran; F.P. Anderson; A. Devery; S. Cloonan; W.E. Butler; S. Varughese; S.M. Draper; P.T.M. Kenny *Bioorg. Med. Chem.* 2009, **17**, 4510.
6. (a) T. Jeffery; B. Ferber *Tetrahedron Lett.* 2003, **44**, 193. (b) M.L. Cardona; M.I. Fernandez; M.B. Garcia; J.R. Pedro *Tetrahedron Lett.* 1986, **42**, 2725. (c) F. Orsini; F. Pelizzoni; L. Verotta; T. Aburjai *J. Nat. Prod.* 1997, **60**, 1082. (d) R. Shirai; H. Takayama; A. Nishkama; Y. Koiso; Y. Hashimoto *Bioorg. Med. Chem. Lett.* 1998, **8**, 1997. (e) G.G. Cross; C.R. Eisnor; R.A. Gossage; H.A. Jenkins *Tetrahedron Lett.* 2006, **47**, 2245. (f) M. Moreno-Manas; R. Pleixats *An. Quim. C* 1985, **81**, 157. (g) E. Alonso; D.J. Ramon; M. Yus *J. Org. Chem.* 1997, **62**, 417. (h) M. Wang; Y. Jin; C.T. Ho *J. Agric. Food. Chem.* 1999, **43**, 2941.
7. (a) M. Guiso; C. Marra; A. Farina *Tetrahedron Lett.* 2002, **43**, 597. (b) A. Farina; C. Ferranti; C. Marra *Nat. Prod. Res.* 2006, **20**, 247. (c) T. Jeffery; B. Ferber *Tetrahedron Lett.* 2003, **44**, 193. (d) M.B. Andrus; J. Liu; E.L. Meredith; E. Nartey *Tetrahedron Lett.* 2003, **44**, 4819. (e) L. Botella; C. Nájera *Tetrahedron* 2004, **60**, 5563. (f) H. Lebel; C. Ladjel; L. Bréthous *J. Am. Chem. Soc.* 2007, **129**, 13321. (g) T. Iijima; H. Makabe *Biosci. Biotech. Bioch.* 2009, **73**, 2547. (h) B. Schmidt; N. Elizarov; R. Berger; F. Hölter *Org. Biomol. Chem.* 2013, **11**, 3674.
8. (a) K. Ferre-Filmon; L. Delaude; A. Demonceau; A.F. Noels, *Eur. J. Org. Chem.* 2005, 3319. (b) J. Velder; S. Ritter; J. Lex; H.-G. Schmalz *Synthesis* 2006, 273.
9. G. P. Roth and V. Farina, *Tetrahedron Lett.* 1995, **36**, 2191.
10. M. S. Kabir, A. Monte and J. M. Cook, *Tetrahedron Lett.* 2007, **48**, 7269.
11. M.-A. Bazin; L.E. Kihel; J.-C. Lancelot; S. Rault *Tetrahedron Lett.* 2007, **48**, 4347.
12. K. Ferré-Filmon; L. Delaude; A.O. Demonaceau; A.F. Noels *Coord. Chem. Rev.* 2004, **248**, 2323.
13. A.V. Moro; F.S.P. Cardoso; C.R.D. Correia *Tetrahedron Lett.* 2008, **49**, 5668.
14. Last access on May 19, 2014: http://www.bgrci.de/fileadmin/BGRCI/Downloads/DL_Praevention/Fachwissen/Gefahrstoffe/TOXIKOLOGISCHE_BEWERTUNGEN/Bewertungen/ToxBew260-E.pdf
15. (a) I. Peñafiel; I.M. Pastor; M. Yus *Eur. J. Org. Chem.* 2012, 3151. (b) V.K. Aggarwal; A.C. Staubitz; M. Owen *Org. Process Res. Dev.* 2006, **10**, 64. (c) For a theoretical introduction, see: G.E.P. Box; W.G. Hunter; J.S. Hunter Statistics for Experiments - *An Introduction to Design, Data Analysis, and Model Building*; Wiley: New York, 1978. (d) G.E.P. Box; N.R. *Draper Empirical Model-Building and Response Surfaces*; Wiley: New York, 1987.
16. The calculations were performed using a commercially available computer program: Minitab®, version 16.2.0; Quality Plaza, 1829, Pine Hall Rd, State College PA, 16801-3210, USA.
17. Y. Takahashi; T. Ito; S. Sakai; Y. Ishii *J. Chem. Soc.Chem. Commun.* 1970, 1065.
18. D.F. Aycock *Org. Process Res. Dev.* 2007, **11**, 156.
19. Lee, J.-K.; Schrock, R.R.; Baigent, D.R.; Friend, R.H. *Macromolecules* 1996, **28**, 1966.
20. McNulty, J.; Das, P.; McLeod, D. *Chem. Eur. J.* 2010, **16**, 6756.
21. Li, X.-B.; Wang, L.; Zhang, X.Q.; Gu, H.M.; Guo, J.; Li, B.-L. *J. Chem. Res.* 2010, 489.
22. Fumagalli, T.; Sello, G.; Orsini, F. *Synth. Commun.* 2009, **39**: 2178.
23. McNulty, J.; Das, P. *Eur. J. Org. Chem.*, 2009, 4031.
24. Woods, J.A.; Hadfield, J.A.; Pettit, G.R.; Fox, B.W.; McGown, A.T. *British Journal of Cancer* 1995, **71**, 705.

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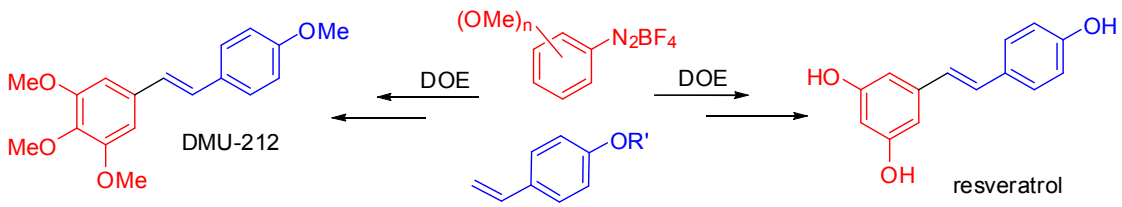

Design of experiments (DOE) was instrumental to optimize reaction conditions which allowed the efficient synthesis of key bioactive stilbenes.

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