Toward the Synthesis of Caraphenol C: Substituent Effect on the Nazarov Cyclization of 2-Arylchalcones

Jun Zhu,[a] Chen Zhong,[a] Hong-Fu Lu,[a] Guang-Yu Li,[b] Xun Sun*[a]

[a] Department of Chemistry of Natural Drugs, School of Pharmacy, Fudan University, 138 Yixueyuan Road, Shanghai 200032, P. R. of China
Fax +86(21)54237607; E-mail: sunxunf@shmu.edu.cn

[b] Laboratory of Analytical Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. of China

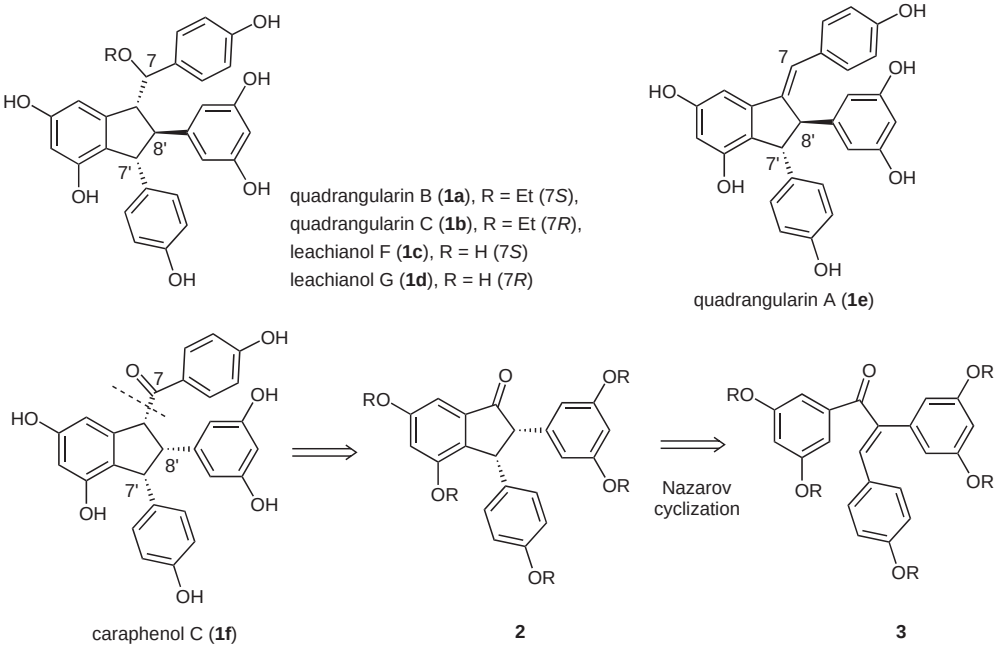
Received 24 September 2007

Abstract: A mild and versatile synthesis of *cis*-2,3-diarylindanones using a Nazarov cyclization strategy was reported. The substituent effect on the stereochemistry of the cyclization was discussed.

Key words: caraphenol C, chalcone, 2,3-diarylindanone, Lewis acid, Nazarov cyclization

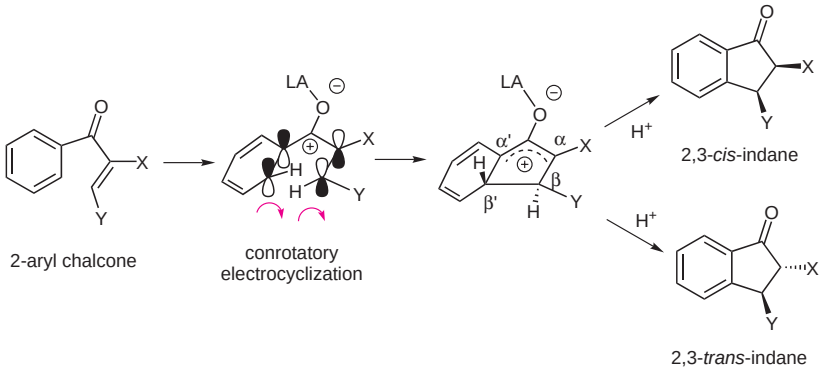
The Nazarov cyclization is recognized as one of the most powerful methods for the synthesis of five-membered carbocycles due to its prevalence in numerous natural products and bioactive compounds.[1] To meet the need in syntheses and structural modifications, the Nazarov cyclization has spurred efforts to realize the ring closure of alkyl-substituted bisvinyl ketones. Surprisingly, α-arylchalcone was scarcely subjected to this cyclization to form 2,3-diarylindanone. In the literature, the synthesis of 2,3-diarylindanone was realized by a ring enlargement of 3-methoxy-1,2,3-triphenylcyclopropene,[2] cyclization of 2,3,3-triphenylpropanoyl chloride,[3] or hydrogenation of 2,3-diarylindenone with palladium on charcoal.[4] The Nazarov cyclization of 2-arylchalcone was recently realized by the Marco and Flynn groups in which Lewis acid or protic acid was utilized to give *trans*-2,3-diphenylindan-1-one in excellent yield.[5] In the context of total syntheses of dimeric resveratrols, we envisioned that the Nazarov cyclization could be a powerful approach to 2,3-substituted indanone moieties. We wish to present here mild and versatile reaction conditions to pursue the stereoselective synthesis of *cis*-2,3-diarylindanone moiety presented in caraphenol C, and clarify the substituent effect on the stereochemistry of the Nazarov cyclization.

Caraphenol C was first isolated from the dry roots of *Caragana sinica*, a Chinese folk medicine for the treatment of asthenia syndrome, vascular hypertension, leukorrhagia,

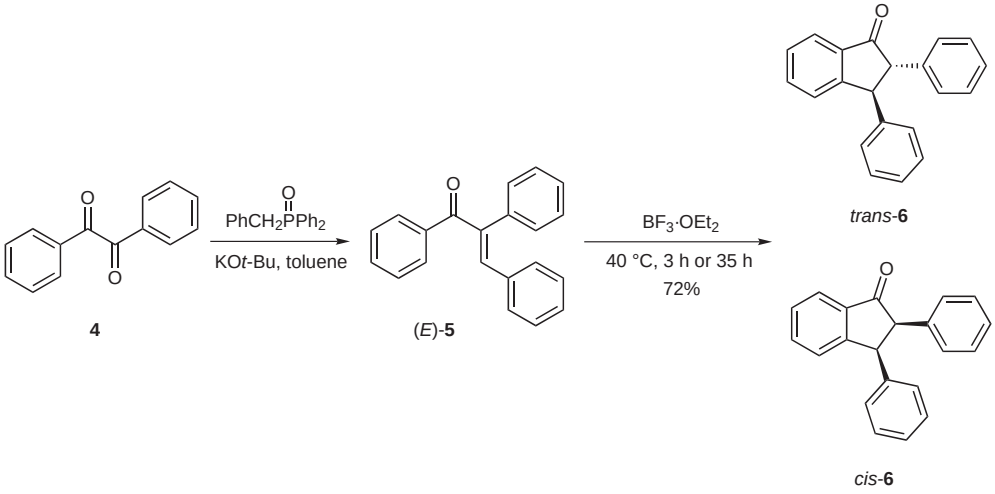


Scheme 1 Selected resveratrol dimers and retrosynthetic analysis of caraphenol C

SYNLETT 2008, No. 3, pp 0458–0462
Advanced online publication: 03.01.2008
DOI: 10.1055/s-2008-1032065; Art ID: W17707ST



Scheme 2 The mechanism of Nazarov cyclization



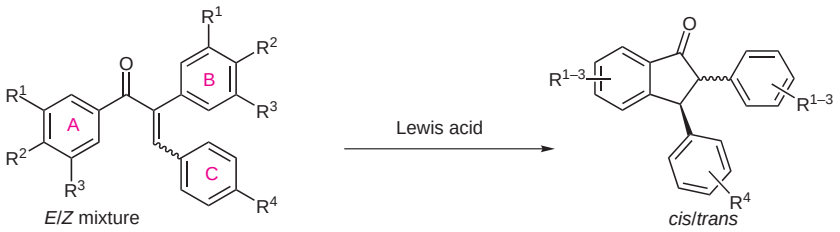
Scheme 3 The Nazarov cyclization of (*E*)-2-phenylchalcone (**5**)

bruises, and contused wounds.[6] The *cis*-configuration of C7′ and C8′ in caraphenol C differs from those of other resveratrol dimers, such as quadrangularins A–C and leachianols F, G (Scheme 1).[7]

A recent biomimetic approach toward quadrangularin A by Hou and co-workers represented a concise synthetic strategy to construct the 2,3-*trans*-indane skeleton.[8] However, the radical coupling only provided 2,3-*trans*-indanes. From the mechanistic point of view, the 2,3-*cis*-indanone **2** skeleton in caraphenol C could be achieved with a delicately controlled protonation step during the Nazarov cyclization of **3** (Scheme 2).[1,9] To this end, (*E*)-2-phenylchalcone **5**, prepared from the Wittig–Horner reaction of benzil **4** with $Ph_2P(O)CH_2Ph$ in the presence of KO*t*-Bu in toluene, was subjected to the Nazarov cyclization in the presence of $BF_3{\cdot}OEt_2$ (Scheme 3). Although Marco reported the exclusive *trans*-indanone **6** was isolated when the 2-phenylchalcone *trans*-**5** was treated with Lewis acid,[5a] another product (minor) was generated in our entry along with the *trans*-isomer of **6**. This minor product was identified as the *cis*-isomer of **6** ($^3J_{H2–H3}$ = 8.1 Hz) by ^{1}H NMR analysis, which was identical with the literature data.[10] This *cis*-isomer of **6** could be detected by TLC analysis when approximately 20% of the starting material was consumed (monitored by ^{1}H NMR). However, after all the starting material was consumed, only the *trans*-isomer **6** ($^3J_{H2–H3}$ = 4.7 Hz) was isolated, as reported previously by Marco.[5a] Attempt to purify *cis*-indanone **6** was not successful due to its rapid epimerization to *trans*-isomer of **6** on silica gel.

To further identify the stability of the 2,3-*cis*-indanone during the cyclization event, a series of 2-arylchalcones were synthesized and subjected to cyclization conditions as shown in Table 1. In order to promote the cyclization of chalcones bearing electron-withdrawing groups at A and B rings, such as **7a**,**b**, $AlCl_3$ was used as the promoter as $BF_3{\cdot}OEt_2$ was ineffective. Only *trans*-products **8a**,**b** were isolated after the chalcones **7a**,**b** were consumed (entries 1 and 2). The moderate isolated yields of **8a** and **8b** were due to the considerable decomposition of substance under the harsher reaction conditions ($AlCl_3$, 40 °C). On the other hand, electron-donating groups (OMe and Me) at the *para* positions of A and B rings enhanced the reaction efficiency to give higher yields of products **8c** and **8d** under milder reaction conditions ($BF_3{\cdot}OEt_2$, entries 3 and 4, respectively). An interesting finding was noted with the *meta*-methoxy in **7e**. Boron trifluoride diethyl etherate promoted cyclization of **7e** to furnish the *cis*-product in 82% yield within 20 minutes (entry 5), but the *trans*-isomer was formed in 96% after prolonging the

Table 1 The Nazarov Cyclization of 2-Arylchalcones to 2-Arylindanones



7a–g **8a–g**

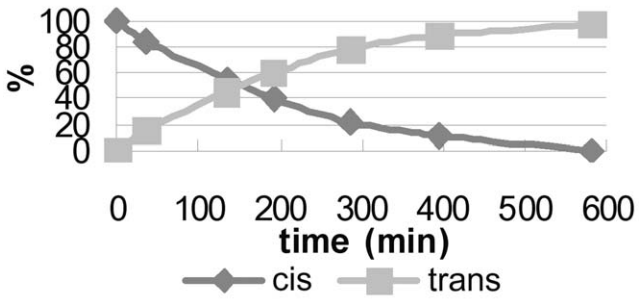
Entry	Substrate	R^1	R^2	R^3	R^4	Conditions[a]	Time	Temp (°C)	Product (yield)[e]
1	**7a**	H	H	H	H	A (4 equiv)[b]	70 h	40[c]	**8a** (*trans*, 24%)[f]
2	**7b**	H	H	H	H	A (10 equiv)	47 h	40[c]	**8b** (*trans*, 50%)[f]
3	**7c**	H	OMe	H	H	B	40 h	r.t.[d]	**8c** (*trans*, 89%)[g]
4	**7d**	H	OMe	H	H	B	17 h	40	**8d** (*trans*, 90%)[g]
5	**7e**	OMe	H	H	H	B	20 min	r.t.	**8e** (*cis*, 82%)[h]
6	**7e**	OMe	H	H	H	B	11 h	40	**8e** (*trans*, 96%)
7	**7f**	OMe	H	OMe	H	B	13 min	r.t.	**8f** (*cis*, 76%)[h]
8	**7f**	OMe	H	OMe	H	B	11 h	40	**8f** (*trans*, 94%)
9	**7g**	OMe	H	OMe	OMe	B	7 min	r.t.	**8g** (*cis*, 94%)[h]
10	**7g**	OMe	H	OMe	OMe	B	12 h	40	**8g** (*trans*, 85%)

[a] Conditions A: 2-arylchalcone (1 equiv), $AlCl_3$ (4 or 10 equiv), CH_2Cl_2. Conditions B: 2-arylchalcone (1 equiv), $BF_3{\cdot}OEt_2$ (10 equiv), CH_2Cl_2.
[b] $AlCl_3$ was added in portions by single equivalent until the reaction went into completion.
[c] No reaction at r.t.
[d] A comparable yield was achieved at 40 °C in 10 h.
[e] All the yields of *trans*-products were given after flash column chromatography while those of *cis*-products were obtained after trituration.
[f] Besides some degraded polar compounds, only *trans*-products were isolated in entries 1 and 2.
[g] The corresponding spot of *cis*-product could be observed on TLC within a short period of reaction time (together with the spot of *trans*-product), but only *trans*-product remained when reaction went into completion. Even when the *cis*-product still remained, only *trans*-product could be isolated after flash column chromatography.
[h] The minor *trans*-indanone can be removed by trituation, see ref.13 for detail.

reaction to 11 hours. For entries 7–10, more methoxy groups were introduced to the A, B, and C phenyl rings. The faster cyclizations allowed us to isolate the *cis*-products **8f** and **8g**, and not surprisingly, epimerization to the *trans*-isomers was anticipated with an extended reaction time (entries 7–10). The half-life of the *cis*-to-*trans* epimerization of **8g** at 40 °C was approximately 155 minutes in the presence of $BF_3{\cdot}OEt_2$ (10 equiv, Table 2). The *para*-methoxy in C ring of **7g** (entry 9) gave a *cis*-indanone **8g** which could be used as an intermediate toward an efficient synthesis of caraphenol C.

A possible mechanism for the electrocyclization of the 2-arylchalcones was illustrated in Scheme 4. In the Nazarov cyclization, the key step is believed to be the cyclization of a 4π-electron system through a conrotatory (under thermal conditions) electrocyclic process to form a five-membered ring.[11] The mechanism of the Nazarov reaction is well known at an experimental as well as theoretical level.[12] It proceeds via a rate-determining electrocyclization to a relatively high-energy intermediate that can be represented by, in this case, contributing resonance forms **7-II** and **7-III** or by the hybrid resonance form **7-I** for simplicity. The electronic effect of substituted groups at phenyl rings A and B had a profound effect on reaction rate in the Nazarov cyclization of 2-arylchalcones. Obviously, the electron-donating groups that stabilize the developing positive-charge character will lower the energy of the intermediate (and transition state), thereby enhancing the rate of the cyclization. After cyclization, the second step is the tautomerization of ketone–enol to produce the *cis*- and *trans*-cyclopentenone products and the steric hindrance of the phenyl ring C at the β-position can affect the stereochemical outcome of the cyclization. For example, if R^1 was a *meta* electron-donating group (such as in entries 5, 7, and 9), the 2-arylchalcone cyclized faster and the electronegativity at the α-postion of **8-I** was enhanced which made it easier to abstract a proton. Therefore the kinetic product *cis*-**8** was generated as the major product within a short time. As reaction time was prolonged, a

Table 2 The Kinetics of *cis*-**8g** to *trans*-**8g**



Time (min)[a]	*cis*-**8g** (%)[b]	*trans*-**8g** (%)
0	100	0
36	84	16
134	55.2	44.8
191	40	60
286	21.7	78.3
394	11.7	88.3
581	2.7	97.3

[a] Reaction conditions: To a solution of *cis*-**8g** (120 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}OEt_2$ (0.35 mL, 2.8 mmol) under a nitrogen atmosphere at 40 °C.
[b] The isomer ratios were measured with ^1H NMR by comparing the chosen proton peak area.

thermodynamic product *trans*-**8** was finally obtained as a result of its thermodynamic stability.[13]

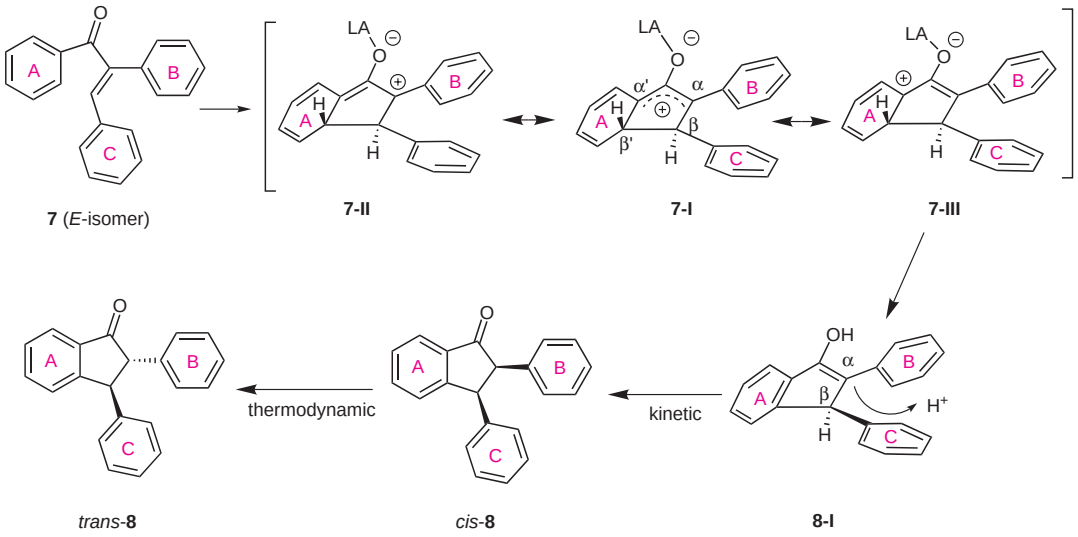
In summary, the success formation of *cis*-2,3-diarylindanone was mainly relied on the electron-donating groups at arenes and the steric hindrance of the substituent at the β-postion. Further investigations on the Nazarov cyclization of 2-arylchalcones in the context of total synthesis of caraphenol C are currently under way.

Acknowledgment

Financial support by the National Natural Science Foundation of China (20772017) and the Shanghai Municipal Committee of Science and Technology (05JC14057 and 07DZ19713) is acknowledged. We are grateful to Dr. Ran Hong of the Laboratory of Modern Synthetic Organic Chemistry at Shanghai Institute of Organic Chemistry (CAS) for invaluable discussions.

References and Notes

(1) Reviews: (a) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.
(2) Mueller, P.; Pautex, N. *Helv. Chim. Acta* **1991**, *74*, 55.
(3) Rockett, B. W.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 1394.
(4) Pettit, W. A.; Wilson, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 6372.
(5) (a) Marco, J. L. *Synth. Commun.* **1996**, *26*, 4225. (b) Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* **2003**, 1380.
(6) Luo, H.-F.; Zhang, L.-P.; Hu, C.-Q. *Tetrahedron* **2001**, *57*, 4849.
(7) (a) Adesanya, S. A.; Nia, R.; Martin, M.-T.; Boukamcha, N.; Montagnac, A.; Pais, M. *J. Nat. Prod.* **1999**, *62*, 1694. (b) Ohyama, M.; Tanaka, T.; Iinuma, M. *Phytochemistry* **1995**, *38*, 733.
(8) Li, W.; Li, H.; Li, Y.; Hou, Z. *Angew. Chem. Int. Ed.* **2006**, *45*, 7609.
(9) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544.
(10) Hiscock, M.; Porter, G. B. *J. Chem. Soc. B* **1971**, 1631.
(11) See the reviews: (a) Denmark, S. E. *Nazarov and Related Cationic Cyclizations*, In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford, UK, **1991**, 751–784. (b) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *The Nazarov Cyclization*, In *Organic Reactions*, Vol. 45; Paquette, L. A., Ed.; Wiley: New York, **1994**, 1–158.



Scheme 4 Proposed mechanism for electrocyclization of 2-arylchalcones

(12) (a) Smith, D. A.; Ulmer, C. W. *J. Org. Chem.* **1991**, *56*, 4444. (b) Smith, D. A.; Ulmer, C. W. *Tetrahedron Lett.* **1991**, *32*, 725. (c) Smith, D. A.; Ulmer, C. W. *J. Org. Chem.* **1993**, *58*, 4118. (d) Smith, D. A.; Ulmer, C. W. *J. Org. Chem.* **1997**, *62*, 5110. (e) Faza, O. N.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *Chem. Eur. J.* **2004**, *10*, 4324. (f) Cavalli, A.; Masetti, M.; Recanatini, M.; Prandi, C.; Guarna, A.; Occhiato, E. G. *Chem. Eur. J.* **2006**, *12*, 2836. (g) Polo, V.; Andres, J. *J. Chem. Theory Comput.* **2007**, *3*, 816.

(13) **General Procedure for the Synthesis of 2-(3,5-dimethoxyphenyl)-4,6-dimethoxy-3-(4-methoxyphenyl)-2,3-dihydroinden-1-one**

Compound *cis*-8g

To a solution of α-substituted chalcones **7g** (2.78 g, 6.40 mmol) in CH_2Cl_2 (70 mL) was added dropwise $BF_3{\cdot}OEt_2$ (8.11 mL, 64 mmol) via syringe. After the reaction mixture was stirred at r.t. for 7 min under a nitrogen atmosphere, the reaction was quenched by the addition of H_2O (60 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phase was washed with brine and dried over anhyd Na_2SO_4. After removal of solvent, the resulting yellow residue was washed by the solution of EtOAc in PE (1–2%). The pure product *cis*-**8g** (2.6 g, 94%) was obtained after trituration as a white solid; mp 146–148 °C. IR (KBr): ν_{max} = 2837, 1705, 1608, 1596, 1512, 1150 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.56 (s, 6 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 3.91 (s, 3 H), 4.27 (d, 1 H, *J* = 7.8 Hz), 4.92 (d, 1 H, *J* = 7.8 Hz), 5.90–7.26 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.3, 55.1, 55.67, 55.7, 55.8, 61.9, 96.1, 99.3, 106.2, 108.4, 113.0, 129.3, 132.4, 136.7, 138.3, 139.0, 157.6, 158.0, 160.0, 161.7, 205.4 ppm. MS (EI): *m/z* (%) = 434 (100) [M^+] , 326 (25.54) [$M^+ - PhOCH_3$].

Compound *trans*-8g

To a solution of α-substituted chalcones **7g** (3.21 g, 7.40 mmol) in CH_2Cl_2 (100 mL) was added dropwise $BF_3{\cdot}OEt_2$ (9.38 mL, 74 mmol). After the reaction solution was stirred for 40 h at r.t. under a nitrogen atmosphere, the reaction mixture was quenched by the addition of H_2O (80 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic phase was washed with brine and dried over anhyd Na_2SO_4. After removal of solvent, the residue was subjected to purification on silica gel by flash column chromatography (PE–EtOAc, 5:1) to afford the pure product *trans*-**8g** (2.68 g, 85%) as a white solid; mp 168–169 °C. IR (KBr): ν_{max} = 2937, 2840, 1711, 1610, 1514, 1202, 1156 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.60 (d, 1 H, *J* = 3.0 Hz, 3-H), 3.66 (s, 3 H, OCH_3), 3.73 (s, 6 H, 2 × OCH_3), 3.78 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.51 (d, 1 H, *J* = 3.0Hz, 2-H), 6.23–6.95 (m, 9 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.8, 55.2, 55.3, 55.6, 55.8, 65.3, 96.4, 98.9, 106.0, 106.6, 113.8, 127.9, 128.1, 135.4, 138.5, 141.5, 157.7, 158.1, 160.9, 161.9, 205.5. MS (EI): *m/z* (%) = 434 (100) [M^+] , 326 (22.59) [$M^+ - CH_3OPhCH$]. HRMS (EI): *m/z* calcd for $C_{26}H_{26}O_6$: 434.1721; found: 434.1713.