Tetrahedron 68 (2012) 5216–5222

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tf_2O-catalyzed Friedel–Crafts alkylation to synthesize dibenzo[*a*,*d*]cycloheptene cores and application in the total synthesis of Diptoindonesin D, Pauciflorial F, and (±)-Ampelopsin B

Gang-Wei Wang [a], Hong-Li Wang [a], David A. Capretto [b], Qi Han [a], Rong-Bin Hu [a], Shang-Dong Yang [a,*]

[a] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Tianshui South Road 222, Lanzhou 730000, PR China
[b] Department of Chemistry, University of Chicago, 929 East 57th Street, Chicago, IL 60637, USA

ARTICLE INFO

Article history:
Received 21 December 2011
Received in revised form 12 March 2012
Accepted 20 March 2012
Available online 30 March 2012

Keywords:
Tf_2O
Friedel–Crafts alkylation
Dibenzo[*a*,*d*]cycloheptene
Diptoindonesin D
(±)-Ampelopsin B

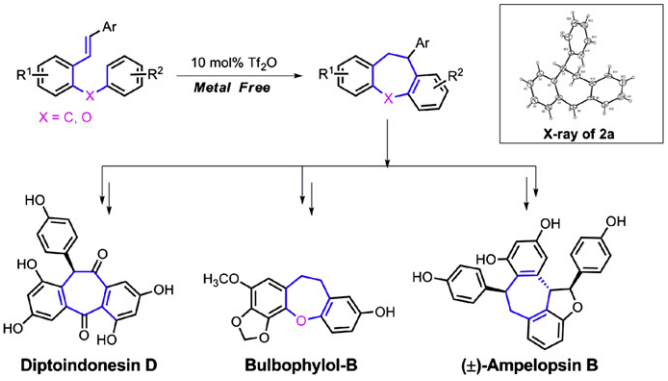
ABSTRACT

By using Tf_2O as a catalyst, we have developed a protocol for the preparation of various dibenzo[*a*,*d*]cycloheptene cores via Friedel–Crafts alkylation. Using this method as the key step, we also present concise and useful routes to synthesize the natural products Diptoindonesin D, Pauciflorial F, and (±)-Ampelopsin B. Notably, this process exhibited following very attractive features: (i) the process is metal free, with only catalytic amounts of Tf_2O being employed, and (ii) the process is simple and environmentally conscious, avoiding the use of excess amounts of base, oxidant, or other additives.

1. Introduction

The dibenzo[*a*,*d*]cycloheptene framework is one type of polycyclic skeleton that exists extensively in many natural products.[1] As a consequence; many strategies have been developed for the synthesis of this framework. One of the most straightforward methods is the intramolecular Friedel–Crafts acylation reaction.[2] Another popular synthetic route is the equivalent acid-catalyzed Friedel–-Crafts alkylation of olefins.[3] Recently, Stoltz and co-workers developed a novel approach to dibenzo[*a*,*d*]cycloheptene core structures by benzyne insertion into the α,β C–C single bond of an α-ketoester.[4] However, all the aforementioned methods either require stoichiometric metal salts/acids in unfavorable conditions or require a specifically functionalized precursor, which limits scope. Thus, the development of new and more efficient method is attractive.

Lewis acid-catalyzed direct C–H transformation provides a highly valuable strategy for C–C coupling reactions because of its wide substrate scope and high atom economy.[5] Herein, we describe a versatile method to construct dibenzo[*a*,*d*]cycloheptene cores by Tf_2O-catalyzed intramolecular cyclization of alkenyl substrates via Friedel–Crafts alkylation (Scheme 1). Using this method as the key step, we also present concise and useful routes to synthesize the natural products Diptoindonesin D, Pauciflorial F, and (±)-Ampelopsin B. In addition, this reaction displays some very attractive features: (i) the process is metal free, with only catalytic amounts of Tf_2O being employed, and (ii) the process is simple and environmentally conscious, avoiding the use of excess amounts of base, oxidant, or other additives.



Scheme 1. Tf_2O-catalyzed dibenzo[*a*,*d*]cycloheptene synthesis and the resulting natural products.

* Corresponding author. E-mail address: yangshd@lzu.edu.cn (S.-D. Yang).

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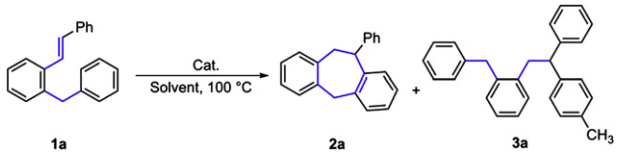
doi:10.1016/j.tet.2012.03.073

2. Results and discussion

We previously found that platinum-catalyzed the intramolecular cyclization of *o*-isopropyl or *o*-benzyl arylalkynes into functionalized indenes through sp^3 C–H bond activation.[6] Inspired by these results, we wished to extend this method to *o*-benzyl alkenyl substrates. Disappointingly, results indicated that similar platinum salts were completely ineffective in this reaction. After further screening of catalysts, we found that the use of 10 mol % $FeBr_2$ and 20 mol % $Cu(OTf)_2$ as co-catalyst yielded unexpected products. Dibenzo[*a*,*d*]cycloheptene was obtained in 92% yield with high regioselectivity. To prove our hypothesized connectivity, we collected X-ray diffraction data of **2a** and showed that our analysis was correct (Scheme 1).[7] However, we were still confused about the role of $Cu(OTf)_2$ in this transformation. In order to clarify, we further tested different proton and Lewis acids. We found that TfOH could catalyze this reaction very well, but the regioselectivity was poor and byproduct **3a** was obtained in 18% yield (Table 1, entry 1). The screening of different acids and anhydrides (Table 1, entries 3–10) revealed that Tf_2O gave the best result, yielding 95% of **2a**. Decreasing the catalyst loading to 5 mol % lowered the yield of **2a** to 82% (Table 1, entry 11). Solvent screening showed that toluene and DCE were optimal.

Table 1
Cyclization condition screening[a]



Entry	Cat. [mol %]	Solvent	*t* [h]	Yield **2a**[b] [%]	Yield **3a**[b] [%]
1	TfOH 10%	Toluene	6	77%	18%
2	TfOH 20%	Toluene	6	69%	23%
3	CF_3CO_2H 10%	Toluene	10	N.R.[c]	N.R.[c]
4	$BF_3{\cdot}Et_2O$ 20%	Toluene	10	N.R.[c]	N.R.[c]
5	HBF_4 10%	Toluene	10	N.R.[c]	N.R.[c]
6	CH_3SO_3H10%	Toluene	10	N.R.[c]	N.R.[c]
7	$TiCl_4$ 10%	Toluene	10	20%	<1%
8	$(CH_3SO_2)_2O$10%	Toluene	10	N.R.[c]	N.R.[c]
9	**Tf_2O 10%**	**Toluene**	**10**	**95%**	**<1%**
10	Ac_2O 10%	Toluene	10	N.R.[c]	N.R.[c]
11	Tf_2O 5%	Toluene	10	82%	<1%
12	Tf_2O 10%	DCE	12	69%	—

The data in bold font represents the optimized reaction conditions.
[a] All reactions were carried out in the presence of 0.5 mmol of **1a** in 5 mL solvent at 100 °C.
[b] The isolated yield.
[c] N.R. is no reaction.

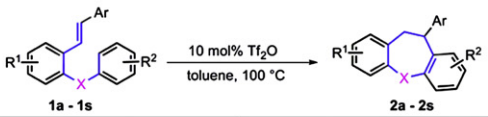
Under the optimized conditions, we surveyed various alkenes (Table 2). The dibenzo[*a*,*d*]cycloheptene derivatives **2a**–**s** produced products in moderate to excellent yields and high selectivity. Electronic effects were not evident in this reaction; high yields were observed with both electron-withdrawing and electron-donating groups present on the phenyl ring. However, the use of **2f** and **2i** only obtained moderate yields (69% and 55%, respectively). When the X is an oxygen atom, the reaction also worked smoothly and products of **2g** and **2h** were yielded in 88% and 76% yield, respectively. In addition, the polymethoxyl substituted products of **2l** and **2q**–**r** were obtained in low to good yields. If the benzylic portion was substituted with a hydroxyl group, dehydration occurred and the poly-substituted indene product **2s** was obtained in 31% yield. Unfortunately, heterocycles, such as pyrrole, indole, and pyridine yielded no observable product.

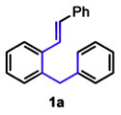
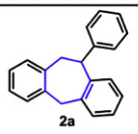
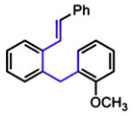
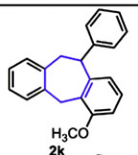
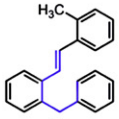
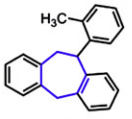
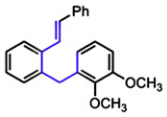
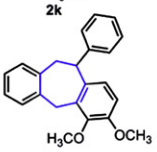
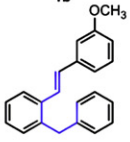
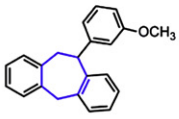
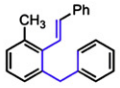
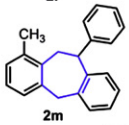
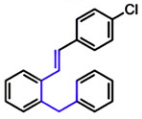
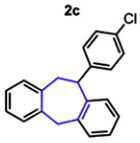
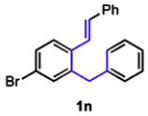
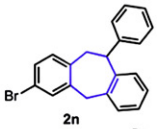
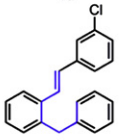
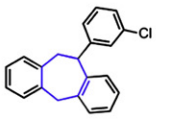
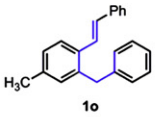
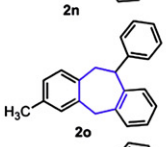
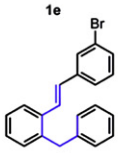
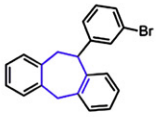
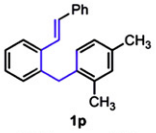
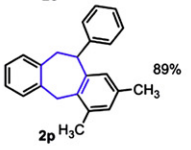
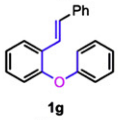
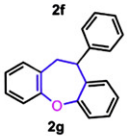
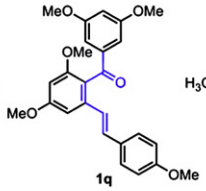
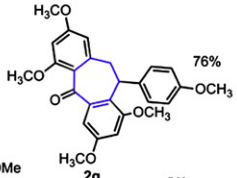
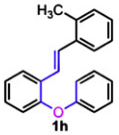
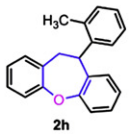
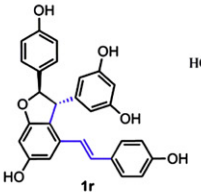
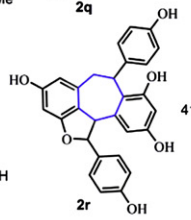
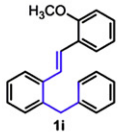
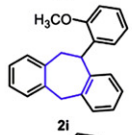
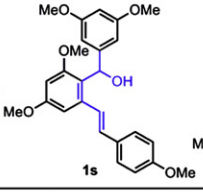
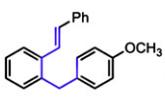
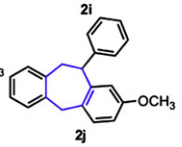
As resveratrol-based oligomers, the polyphenol natural products Diptoindonesin D, (±)-Ampelopsin B, and Paucifloral F exhibit a wide variety of pharmacological activities including anti-inflammatory, antioxidant, antifungal, antibacterial, anti-HIV, and anticarcinogenic activities.[8] Despite their interesting biological activities as well as their unique carbon framework, few synthetic approaches toward these types of compounds have been reported.[9] In order to display the utility of our chemistry, we applied our method in the synthesis of the natural products Diptoindonesin D, Paucifloral F (Scheme 2, part A), and (±)-Ampelopsin B (Scheme 2, part B). Our strategy to synthesize Diptoindonesin D and Paucifloral F began with the preparation of the biaryl alcohol **1s**, which was synthesized in 86% yield through an aldol reaction by the lithiated form of the methyl protected resveratrol bromide **1** and 3,5-dimethoxy benzaldehyde **2** (Scheme 2, part A).[10] Using this key intermediate as the substrate, we directly synthesized the poly-substituted indene **2s** in the presence of 10 mol % Tf_2O as catalyst by Friedel–Crafts alkylation. Oxidation of **2s** followed by deprotection yielded Paucifloral F. On the other hand, **1r** was first oxidized by Dess–Martin periodinane to afford ketone **1q** in 90% yield.[11] Then the carbocyclic core structure of Diptoindonesin D was produced using our Friedel–Crafts alkylation, producing **2q** in 76% yield. After oxidation and deprotection of **2q**, the related natural product Diptoindonesin D may be synthesized. In addition, our reaction can be used in the total synthesis of the natural product (±)-Ampelopsin B (Scheme 2, part B). Based on our retrosynthetic analysis, we selected resveratrol as the starting material and treatment with $FeCl_3{\cdot}6H_2O$ yielded the product (±)-ε-viniferin through oxidative coupling.[12] Then the natural product (±)-Ampelopsin B was obtained in 41% yield directly using our reaction conditions. Despite the lower yield, our route has only two steps and omits the use of protecting groups.

In order to better understand the mechanism of the reaction, we also tested other terminal substituted alkenes. If the aryl group in **1a** is changed to electron-withdrawing groups, such as COOEt, CN, and $COCH_3$, the reaction does not work. However, when the substrate is 1-benzyl-2-vinylbenzene **4a**, the reaction proceeds smoothly and the unexpected product **4ab** is obtained in 38% yield, with the minor product 9-methylanthracene **4aa** (Scheme 3, Eq. 1) formed in low yield. These results show that the formation of the carbocation is the key step in this transformation and the regioselectivity is also determined by it. Based on the structure of substrate **1a** (Scheme 3, Eq. 2), we can see that both **1B** and **2B** are benzylic carbocations, however we did not observed the six membered-ring product at all in the case of **1B**. We believe that the ortho electronic donor effects of the benzyl group lead to a distinction of the energies of **1B** and **2B**, which also ensured the high regioselectivity of reactions. In order to better understand this difference from a thermodynamic perspective and to verify our hypothesis, the relative activation energies of different pathways were studied by DFT calculations with the use of Gaussian98 (B3LYP/6-31G) (Scheme 3, Eq. 2).[13] The results confirmed our hypothesis is logical, and the energy of the benzylic carbocation **1B** is more favorable than **2B**.

In some cases protons rather than metal ions were identified as active catalysts to promote the reaction.[14] In our transformations, Tf_2O may activate trace water and produce protons as catalytic species. The experimental data and activation energy profiles for the considered mechanistic pathways are shown in Scheme 4. The reaction is thought to be initiated by reaction of Tf_2O with trace water to release a proton and coordinate with the alkene to form the cyclic intermediate **1A** (R=Ph, part A). Then, the activated **1A** is transferred to the carbocation **1B** by the release of Tf_2O, which is energetically favored. The Friedel–Crafts alkylation occurs and forms the intermediate **1C**. Finally, deprotonation and aromatization affords the desired product **2a** and releases proton to reinitiate

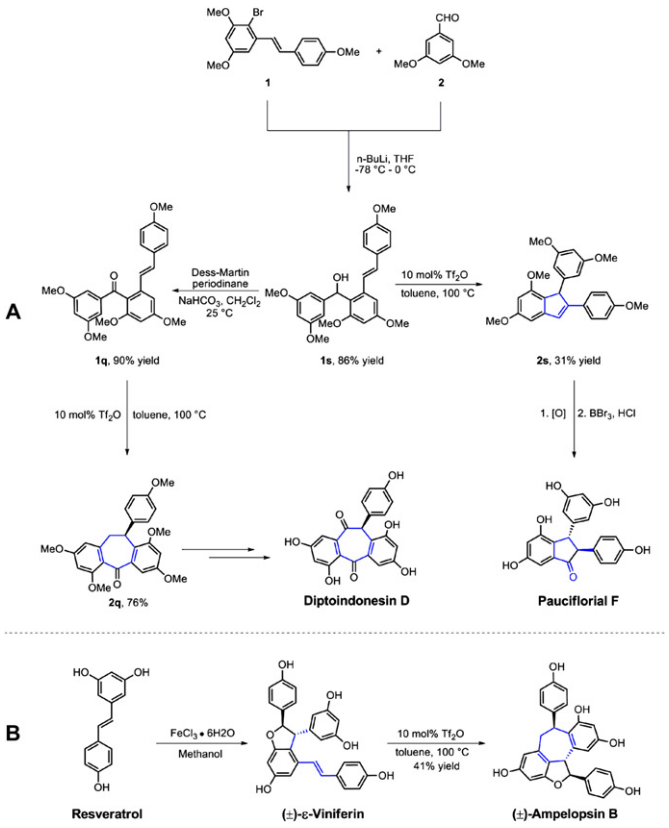
Table 2
Cyclization with different alkenes[a,b]



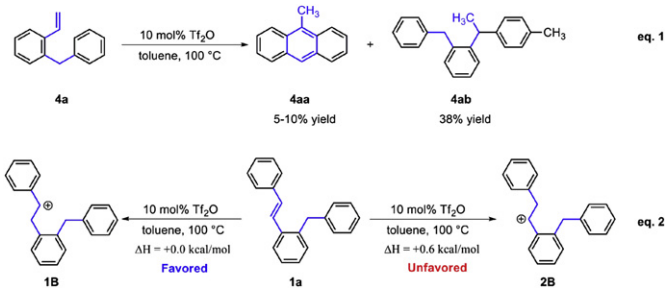
Entry	Substrate	Product	Yield [%]	Entry	Substrate	Product	Yield [%]
1	 1a	 2a	95%	11	 1k	 2k	85%
2	 1b	 2b	92%	12	 1l	 2l	83%
3	 1c	 2c	76%	13	 1m	 2m	92%
4	 1d	 2d	90%	14	 1n	 2n	91%
5	 1e	 2e	80%	15	 1o	 2o	78%
6	 1f	 2f	69%	16	 1p	 2p	89%
7	 1g	 2g	88%	17	 1q	 2q	76%
8	 1h	 2h	76%	18	 1r	 2r	41%
9	 1i	 2i	55%	19	 1s	 2s	31%
10	 1j	 2j	84%				

[a] All reactions were carried out under the optimal conditions reported in the text for 12 h.
[b] The isolated yield.

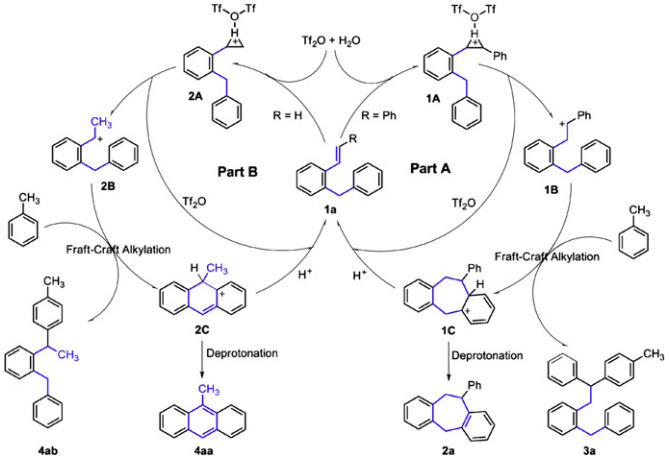
the catalytic cycle. The use of TfOH as catalyst causes some of carbocation **1B** to react with toluene and afford the product **3a**. When the substrate is the 1-benzyl-2-vinylbenzene **4a** (R=H, part B), the first step is same as part A and forms the cyclic intermediate **2A**, then quickly transfers into the benzylic carbocation **2B** by the release of Tf_2O. However, it is very interesting that the Friedel–Crafts alkylation mainly occurs with toluene, forming the product **4ab** as the major product. The intramolecular cyclization product of 9-



Scheme 2. Total synthesis of natural products by Friedel–Crafts alkylation.



Scheme 3. Investigation on cyclization of **4a** and DFT calculations of **1a**.



Scheme 4. The proposed mechanism of Tf_2O-catalyzed cyclization via Friedel–Crafts alkylation.

methylanthracene **4aa** was obtained in only 5–10% yield by aromatic isomerization and the structure was confirmed by X-ray crystallography.[7]

3. Conclusion

By using Tf_2O as a catalyst, we have developed a protocol for the preparation of various dibenzo[*a*,*d*]cycloheptene cores via Friedel–Crafts alkylation. Substrate investigation showed that both electron-donating and withdrawing groups worked smoothly to afford the desired products in moderate to excellent yields. Notably, this process exhibited features of green chemistry. Finally, we used this method in key synthetic steps to synthesis the natural products Diptoindonesin D, Pauciflorial F, and (±)-Ampelopsin B.

4. Experimental section

4.1. General procedure for the Tf_2O-catalyzed Friedel–Crafts alkylation

To a solution of the 1-benzyl-2-styryl-benzene (**1a**) (0.5 mmol) dissolved in 5 mL of toluene in a tube was added 10 mol % of Tf_2O. The solution was stirred for 12 h at 100 °C. Then the reaction was cooled to room temperature and added 20 mL EtOAc. After the organic phase was washed with water and saturated brine. The organic layers were dried over Na_2SO_4, and filtrate was evaporated under reduced pressure. The desired product **2a** was obtained in 95% yields after purification by chromatography on silica gel.

*4.1.1. Compound (**2a**).* White solid; mp: 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–6.97 (m, 12H), 6.83 (d, J=7.6, 1H) 4.50 (t, J_1=7.2, J_2=14.4, 1H), 4.33 (d, J=14.8, 1H), 4.09 (d, J=14.8, 1H), 3.38 (d, J=7.2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.42, 140.81, 140.67, 138.10, 138.02, 132.49, 129.74, 129.27, 128.46, 128.26, 127.78, 126.59, 126.53, 126.50, 126.15, 126.02, 49.20, 41.26, 40.76. IR (neat): 665.22, 698.98, 753.51, 1448.74, 1490.09, 1598.68, 2928.84, 3021.30, 3058.06, 3387.63 cm^{-1}; MS (EI): *m*/*z* (%): 270 (8) [M]$^+$, 192 (100), 179 (41), 178 (30), 193 (19).

*4.1.2. Compound (**2b**).* Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–6.96 (m, 10H), 6.82 (d, J=7.6, 1H), 6.69 (d, J=7.6, 1H), 4.74 (dd, J_1=4.0, J_2=10.8, 1H), 4.40 (d, J=14.8, 1H), 4.11 (d, J=14.8, 1H), 3.42 (dd, J_1=11.2, J_2=14.0, 1H), 3.22 (dd, J_1=4.4, J_2=14.4, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.53, 141.49, 140.41, 138.41, 138.14, 134.94, 131.58, 130.30, 129.54, 129.23, 129.11, 127.97, 126.69, 126.61, 126.51, 126.13, 126.03, 125.97, 44.79, 41.26, 39.20, 19.56. IR (neat): 757.55, 1361.46, 1454.61, 1489.17, 1706.51, 2929.89, 3019.00, 3061.07, 3363.35 cm^{-1}; MS (EI): *m*/*z* (%): 284 (6) [M]$^+$, 192 (100), 179 (31), 178 (27), 193 (21), 191 (17).

*4.1.3. Compound (**2c**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23–6.99 (m, 8H), 6.85 (d, J=7.6, 1H), 6.72 (d, J=8.0, 1H), 6.67 (d, J=7.6, 1H), 6.55 (s, 1H), 4.48 (t, J_1=7.2, J_2=14.4, 1H), 4.32 (d, J=14.8, 1H), 4.09 (d, J=14.8, 1H), 3.69 (s, 3H), 3.38 (d, J=7.2, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.47, 149.00, 140.67, 140.63, 138.09, 137.90, 132.42, 129.73, 129.29, 128.18, 127.77, 126.60, 126.54, 126.50, 126.17, 120.92, 114.46, 111.22, 55.08, 49.17, 41.22, 40.60. IR (neat): 701.41, 761.60, 1046.00, 1259.07, 1455.14, 1487.93, 1599.01, 1708.37, 2835.92, 2936.82, 3019.22, 3057.50, 3377.55 cm^{-1}; MS (EI): *m*/*z* (%): 300 (17) [M]$^+$, 192 (100), 179 (35), 178 (31), 191 (28), 193 (20).

*4.1.4. Compound (**2d**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23–6.99 (m, 8H), 6.92–6.87 (m, 3H), 6.78 (d, J=7.6, 1H), 4.49 (dd, J_1=4.8, J_2=9.2, 1H), 4.19 (dd, J_1=14.8, J_2=35.2, 2H), 3.42 (dd, J_1=4.4, J_2=14.0, 1H), 3.26 (dd, J_1=9.2, J_2=14.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.79, 140.57, 140.24, 137.91, 137.62, 132.47, 131.74,

129.94, 129.35, 127.84, 126.67, 126.63, 126.61, 126.39, 48.55, 41.23, 40.44. IR (neat): 756.12, 828.69, 1013.96, 1091.59, 1450.71, 1489.01, 1703.50, 2881.98, 2932.62, 3021.14, 3061.56, 3384.53, 3466.46 cm^{-1}; MS (EI): *m*/*z* (%): 304 (3) $[M]^+$, 306 (1), 192 (100), 179 (35), 178 (25), 193 (17), 191 (14).

*4.1.5. Compound (**2e**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.21 (m, 2H), 7.15–6.98 (m, 8H), 6.86–6.79 (m, 2H), 4.48 (dd, J_1=5.2, J_2=9.6, 1H), 4.30 (d, J=14.8, 1H), 4.11 (d, J=14.8, 1H), 3.42–3.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.38, 140.62, 139.90, 137.94, 137.61, 134.01, 132.50, 129.96, 129.48, 129.26, 128.57, 127.84, 126.69, 126.62, 126.45, 126.24, 48.98, 41.18, 40.48. IR (neat): 698.89, 752.47, 777.63, 1080.72, 1094.24, 1487.18, 1569.32, 1593.32, 1709.72, 2884.45, 2933.19, 3021.21, 3060.50, 3334.29, 3474.41 cm^{-1}; MS (EI): *m*/*z* (%): 304 (21) $[M]^+$, 306 (7), 179 (100), 192 (98), 178 (69), 191 (28), 193 (19).

*4.1.6. Compound (**2f**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30 (d, J=0.8, 1H), 7.29–7.00 (m, 9H), 6.95 (d, J=7.2, 1H), 6.87 (d, J=7.6, 1H), 6.19 (d, J=7.6, 1H), 4.47 (dd, J_1=5.2, J_2=13.6, 1H), 4.29 (d, J=14.8, 1H), 4.11 (d, J=14.8, 1H), 3.42–3.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.66, 140.60, 139.85, 137.91, 137.57, 132.50, 131.44, 129.95, 129.78, 129.25, 129.16, 127.82, 127.19, 126.70, 126.68, 126.60, 126.44, 122.31, 48.96, 41.16, 40.48. IR (neat): 701.74, 754.78, 1072.05, 1222.48, 1360.29, 1423.80, 1468.52, 1488.05, 1565.87, 1591.48, 1708.51, 2928.05, 3019.67, 3317.62 cm^{-1}; MS (EI): *m*/*z* (%): 348 (10) $[M]^+$, 350 (10), 192 (100), 179 (90), 178 (68), 191 (29), 193 (20).

*4.1.7. Compound (**2g**).* White solid, mp: 94–96 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26–7.13 (m, 7H), 7.06–7.04 (m, 2H), 6.99–6.90 (m, 3H), 6.84 (d, J=8.0, 1H), 4.56 (dd, J_1=4.0, J_2=8.8, 1H), 3.46–3.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.83, 156.55, 145.43, 132.94, 132.31, 131.53, 130.27, 128.41, 128.29, 127.62, 127.57, 126.35, 124.28, 123.77, 121.41, 120.45, 47.17, 38.19. IR (neat): 700.30, 754.83, 1072.24, 1200.94, 1240.03, 1446.39, 1483.71, 1576.09, 2920.01, 2952.06, 3027.09, 3061.45 cm^{-1}; MS (EI): *m*/*z* (%): 272 (100) $[M]^+$, 178 (62), 194 (49), 195 (47), 181 (44), 165 (39), 271 (36), 255 (19).

*4.1.8. Compound (**2h**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.25–6.91 (m, 9H), 6.91–6.87 (m, 2H), 6.67 (d, J=7.6, 1H), 4.82 (dd, J_1=3.6, J_2=10.4, 1H), 3.46 (dd, J_1=10.4, J_2=14.0, 1H), 3.28 (dd, J_1=3.6, J_2=14.4, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.65, 156.75, 143.26, 135.47, 133.97, 131.54, 131.14, 130.40, 130.32, 128.64, 127.58, 127.47, 136.35, 126.08, 124.25, 124.02, 121.23, 120.56, 42.56, 36.92, 19.56. IR (neat): 748.64, 763.39, 1105.39, 1201.56, 1239.34, 1445.04, 1483.56, 1576.19, 2921.23, 3022.80, 3063.83 cm^{-1}; MS (EI): *m*/*z* (%): 286 (100) $[M]^+$, 178 (56), 181 (60), 194 (54), 195 (42), 271 (40), 192 (31), 165 (31).

*4.1.9. Compound (**2i**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23–6.97 (m, 8H), 6.93–6.73 (m, 3H), 6.40 (d, J=7.6, 1H), 4.92 (dd, J_1=4.4, J_2=9.6, 1H), 4.38 (d, J=14.8, 1H), 4.08 (d, J=14.4, 1H), 3.86 (s, 3H), 3.42 (dd, J_1=10.0, J_2=14.0, 1H), 3.29 (dd, J_1=4.8, J_2=14.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.43, 141.23, 141.07, 138.77, 138.35, 135.95, 132.20, 130.13, 129.49, 129.17, 127.58, 127.02, 126.44, 126.41, 126.33, 125.79, 120.46, 110.61, 55.56, 42.33, 41.26, 38.31. IR (neat): 753.00, 1029.01, 1105.80, 1242.82, 1458.85, 1489.75, 1596.10, 1709.41, 2836.83, 2936.51, 3019.75, 3061.85, 3402.50 cm^{-1}; MS (EI): *m*/*z* (%): 300 (4) $[M]^+$, 192 (100), 179 (27), 178 (20), 193 (18), 191 (15).

*4.1.10. Compound (**2j**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.04 (m, 9H), 6.97 (d, J=7.2, 1H), 6.63–6.61 (m, 1H), 6.37 (d, J=2.8, 1H), 4.45 (dd, J_1=5.6, J_2=9.2, 1H), 4.27 (d, J=14.8, 1H), 4.02 (d, J=14.8, 1H), 3.59 (s, 3H), 3.42–3.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.08, 147.14, 142.03, 140.98, 138.01, 130.66, 130.59, 129.26, 127.63, 126.48, 126.43, 126.05, 117.86, 111.50, 55.05, 49.33, 40.65, 40.35. IR (neat): 701.74, 755.64, 1038.19, 1245.65, 1454.52, 1496.87, 1606.10, 1706.74, 2836.07, 2935.60, 3024.08, 3059.90, 3359.88 cm^{-1}; MS (EI): *m*/*z* (%): 300 (55) $[M]^+$, 192 (100), 222 (88), 178 (62), 179 (62), 209 (56), 191 (31), 165 (26), 91 (20).

*4.1.11. Compound (**2k**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26–7.06 (m, 8H), 6.99–6.92 (m, 2H), 6.70 (d, J=8.0, 1H), 6.43 (d, J=8.0, 1H), 4.56 (dd, J_1=6.0, J_2=8.8, 1H), 4.33 (dd, J_1=15.2, J_2=25.2, 2H), 3.86 (s, 3H), 3.44–3.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.28, 146.94, 142.80, 140.41, 138.50, 129.27, 128.59, 127.50, 126.46, 126.33, 126.30, 126.02, 124.13, 108.30, 55.96, 55.94, 48.79, 40.41, 29.54. IR (neat): 701.77, 757.73, 1076.90, 1253.87, 1453.65, 1491.37, 1582.44, 1707.68, 2837.75, 2931.75, 2931.86, 3023.80, 3060.65, 3398.95 cm^{-1}; MS (EI): *m*/*z* (%): 300 (33) $[M]^+$, 222 (100), 209 (31), 178 (25), 165 (25), 179 (22), 207 (22), 223 (21), 192 (16), 91 (18).

*4.1.12. Compound (**2l**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.28–7.01 (m, 9H), 6.58 (d, J=8.4, 1H), 6.52 (d, J=8.4, 1H), 4.50 (dd, J_1=5.2, J_2=10.4, 1H), 4.33 (dd, J_1=13.2, J_2=22.0, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 3.45–3.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.65, 147.29, 145.61, 140.07, 138.52, 134.41, 132.94, 129.36, 128.50, 127.19, 126.48, 126.46, 126.04, 110.16, 61.05, 55.60, 48.31, 40.62, 30.59. IR (neat): 702.57, 757.91, 1048.96, 1080.35, 1222.69, 1278.91, 1451.24, 1488.77, 1598.95, 1710.20, 2835.37, 2935.41, 3022.41, 3404.30 cm^{-1}; MS (EI): *m*/*z* (%): 330 (100) $[M]^+$, 208 (80), 192 (66), 299 (60), 91 (59), 239 (52), 178 (50), 237 (45).

*4.1.13. Compound (**2m**).* Colorless oil, ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23–7.16 (m, 4H), 7.09–6.92 (m, 7H), 6.82 (d, J=7.6, 2H), 4.51 (dd, J_1=4.4, J_2=9.2, 1H), 4.21 (dd, J_1=15.2 J_2=31.2, 2H), 3.47 (dd, J_1=4.4, J_2=14.4, 1H), 3.32 (dd, J_1=9.6, J_2=14.4, 1H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.45, 141.16, 142.72, 138.15, 136.48, 136.21, 132.49, 129.72, 128.45, 126.55, 126.05, 125.75, 48.46, 41.59, 35.66, 19.57. IR (neat): 702.25, 755.76, 1446.71, 1489.86, 1597.09, 1705.01, 2954.36, 3023.08, 3059.64, 3383.96, 3426.77 cm^{-1}; MS (EI): *m*/*z* (%): 284 (25) $[M]^+$, 206 (100), 178 (35), 193 (33).

*4.1.14. Compound (**2n**).* Yellow solid, mp: 118–120 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37 (s, 1H), 7.36–7.14 (m, 5H), 7.09–6.98 (m, 4H), 6.84–6.08 (m, 2H), 4.48 (dd, J_1=4.8, J_2=9.2, 1H), 4.23 (d, J=14.8, 1H), 4.05 (d, J=14.8, 1H), 3.38–3.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.97, 142.72, 140.50, 137.12, 136.99, 132.55, 130.91, 130.62, 129.79, 129.39, 126.88, 126.34, 126.14, 119.91, 48.84, 40.86, 40.08. IR (neat): 701.73, 756.09, 1448.68, 1486.89, 1594.65, 1702.52, 2926.46, 3024.39, 3059.20, 3369.75 cm^{-1}; MS (EI): *m*/*z* (%): 348 (9) $[M]^+$, 350 (9), 178 (100), 272 (69), 270 (67), 191 (52), 165 (49).

*4.1.15. Compound (**2o**).* Yellow solid, mp: 100–102 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.26–6.97 (m, 9H), 6.90 (s, 2H), 6.82 (d, J=7.6, 1H), 4.47 (dd, J_1=4.8, J_2=9.6, 1H), 4.32 (d, J=14.8, 1H), 4.00 (d, J=14.8, 1H), 3.40–3.28 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.58, 140.89, 140.51, 138.18, 136.01, 134.97, 132.50, 129.65, 129.16, 128.59, 128.45, 128.27, 127.09, 126.55, 126.11, 125.98, 49.37, 41.22, 40.39, 20.99. IR (neat): 700.82, 753.63, 813.33, 1450.12, 1493.04, 1599.82, 2885.30, 2924.93, 3020.53, 3056.10, 3403.06 cm^{-1}; MS (EI): *m*/*z* (%): 284 (19) $[M]^+$, 206 (100), 178 (35), 193 (33).

*4.1.16. Compound (**2p**).* White solid, mp: 109–111 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.30–7.16 (m, 6H), 7.08–7.00 (m, 3H), 6.79 (s, 1H), 6.48 (s, 1H), 4.62 (dd, J_1=6.0, J_2=9.6, 1H), 4.16 (dd, J_1=14.8, J_2=40.8, 2H), 3.46–3.35 (m, 2H), 2.44 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.47, 141.64, 139.62, 138.06, 135.27, 134.74,

134.51, 129.81, 129.46, 129.23, 128.43, 128.32, 126.35, 126.22, 126.07, 48.10, 40.21, 34.21, 21.04, 20.80. IR (neat): 700.80, 751.64, 1031.21, 1448.30, 1488.44, 1640.64, 2859.51, 2919.49, 3021.95, 3058.98, 3386.14 cm^{-1}; MS (EI): *m/z* (%): 298 (22) $[M]^+$, 220 (100), 192 (44), 207 (32), 205 (23), 221 (21), 191 (18), 91 (16).

*4.1.17. Compound (**2q**).* White solid, mp: 138–140 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, J=2.4, 1H), 6.70 (d, J=8.8, 2H), 6.60 (d, J=8.8, 2H), 6.53 (d, J=2.4, 1H), 6.27 (d, J=2.4, 1H), 5.70 (d, J=2.0, 1H), 4.66 (dd, J_1=2.4, J_2=6.8, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.58 (s, 3H), 3.54–3.50 (m, 4H), 2.94 (dd, J_1=6.8, J_2=17.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.87, 161.75, 158.94, 158.68, 157.74, 157.44, 141.38, 138.83, 136.04, 128.43, 125.28, 123.61, 112.99, 105.89, 104.02, 103.30, 97.31, 55.94, 55.51, 55.29, 55.10, 42.85, 40.96. IR (neat): 527.26, 787.78, 834.87, 1057.77, 1156.00, 1206.25, 1248.20, 1323.07, 1340.07, 1461.07, 1508.46, 1601.63, 1662.25, 1712.98, 1765.81, 2840.85, 2932.81, 3001.46 cm^{-1}; HRMS: calculated for $[C_{26}H_{26}O_6]$: 435.1802; found: 435.1812.

*4.1.18. Compound (**2r**).* Brown oil. ^1H NMR (400 MHz, CD_3OD) δ: 7.02 (d, J=8.8, 2H), 6.90 (d, J=8.0, 2H), 6.69 (d, J=4.8, 2H), 6.60 (d, J=4.4, 2H), 6.30–6.27 (m, 2H), 6.09 (d, J=1.6, 1H), 6.01 (d, J=2.0, 1H), 5.66 (d, J=11.6, 1H), 5.13 (d, J=3.6, 1H), 4.05 (d, J=11.6, 1H), 3.54 (dd, J_1=4.0, J_2=17.6, 1H), 3.17 (br d, J=17.2, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ: 160.65, 158.94, 158.91, 157.32, 157.13, 156.13, 143.01, 138.80, 135.63, 131.26, 130.32, 129.05, 123.75, 119.77, 116.30, 115.81, 109.39, 105.41, 101.66, 95.91, 89.13, 49.69, 36.48, 34.17. IR (neat): 835.75, 1012.76, 1081.06, 1132.02, 1174.76, 1235.91, 1367.50, 1447.57, 1513.20, 1603.46, 1699.26, 2925.71, 2958.57, 3559.92 cm^{-1}; HRMS: calculated for $[C_{28}H_{22}O_6]$: 455.1489; found: 455.1491.

*4.1.19. Compound (**2s**).* Colorless oil, ^1H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.41 (m, 2H), 7.05 (d, J=0.8, 1H), 6.79–6.77 (m, 2H), 6.58 (d, J=2.0, 1H), 6.36 (d, J=2.0, 2H), 6.23–6.20 (m, 2H), 4.90 (d, J=0.8, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.68 (s, 6H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.07, 160.31, 159.00, 155.79, 151.58, 145.99, 141.88, 127.90, 127.84, 127.75,125.64, 113.85, 106.62, 98.54, 98.13, 96.33, 55.55, 55.47, 55.18, 55.15, 54.14. HRMS: calculated for $[C_{26}H_{26}O_5]$: 419.1853; found: 419.1860.

*4.1.20. Compound (**4aa**).* Colorless oil, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.32–8.26 (m, 3H), 7.99 (d, J=8, 2H), 7.52–7.43 (m, 4H), 3.09 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.48, 130.13, 130.10, 129.05, 125.32, 125.28, 125.22, 124.79, 124.67, 13.91.

*4.1.21. Compound (**4ab**).* Colorless oil, ^1H NMR (400 MHz, CDCl3) δ: 7.28–7.03 (m, 11H), 6.95 (d, J=8.0, 2H), 4.27 (dd, J_1=7.2, J_2=14.4, 1H), 3.97 (dd, J_1=16.0, J_2=41.2, 2H), 2.28 (s, 3H), 1.49 (d, J=7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.53, 143.22, 140.96, 138.19, 135.29, 130.73, 128.97, 128.71, 128.37, 127.43, 127.40, 126.68, 126.09, 125.91, 39.79, 38.90, 22.26, 20.95. IR (neat): 548.79, 698.31, 732.46, 764.45, 818.51, 1030.59, 1450.90, 1489.95, 1511.53, 1732.99, 2870.11, 2925.18, 2965.73, 3023.50, 3059.01 cm^{-1}; MS (EI): *m/z* (%): 286 (26) $[M]^+$, 179 (100), 178 (46), 193 (46), 194 (44), 180 (22), 91 (19).

4.2. Preparation and characterization of substrates

*4.2.1. Preparation of 1-benzyl-2-styryl-benzene (**1a**).* To a solution of the 1-benzyl-2-iodo-benzene **1** (2–7 mmol) and 2 equiv of vinylbenzene and 2.5 equiv of potassium acetate with 1 equiv of tetrabutyl ammonium bromide dissolved in 10 mL of DMF was added 3.0 mol % of palladium acetate under a nitrogen atmosphere. The solution was stirred for 12 h at 100 °C. When the starting 1-Benzyl-2-iodo-benzene had disappeared (TLC), the mixture extracted with EtOAc (3×20 mL) and water. The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (Petroleum–EtOAc 100:1) to afford **1a** as a white solid in 93% yield.

Compound (**1a**): ^1H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, J=7.6, 1H), 7.41–7.15 (m, 14H), 6.96 (d, J=16.0, 1H), 4.13 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.61, 138.27, 137.54, 136.54, 130.60, 130.41, 128.68, 128.63, 128.49, 127.71, 127.57, 126.81, 126.52, 126.39, 126.05, 125.90, 39.31.

*4.2.2. Preparation of {2,4-dimethoxy-6-[2-(4-methoxy-phenyl)-vinyl]-phenyl}-(3,5-dimethoxy-phenyl)-methanol (**1s**).* *n*-BuLi (37.7 mL, 1.6 M in THF, 60.3 mmol, 1.05 equiv) was added slowly over the course of 5 min to a solution of 2-bromo-1,5-dimethoxy-3-[2-(4-methoxy-phenyl)-vinyl]-benzene (20.0 g, 57.4 mmol, 1.0 equiv) in THF (400 mL) at −78 °C, ultimately yielding a light yellow solution. After 20 min of stirring at −78 °C, a solution of the 3,5-dimethoxy benzaldehyde (9.52 g, 57.4 mmol, 1.0 equiv) in THF (200 mL) was added slowly at −78 °C, and the resultant mixture was stirred for 1 h at −78 °C, warmed slowly to 25 °C, and stirred for an additional 4 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (250 mL), poured into water (100 mL), and extracted with EtOAc (3×1 L). The combined organic layers were then washed with water (300 mL) and brine (300 mL), dried ($MgSO_4$), and concentrated. The resultant light yellow oils crystallized upon standing and were then triturated with EtOAc (3×10 mL) to give the {2,4-dimethoxy-6-[2-(4-methoxy-phenyl)-vinyl]-phenyl}-(3,5-dimethoxy-phenyl)-methanol **1s** as white solid.

Compound (**1s**): ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, J=8.4, 2H), 7.26 (s, 1H), 6.88–6.84 (m, 3H), 6.71 (d, J=2.0, 1H), 6.51 (s, 2H), 6.44 (d, J=2.0, 1H), 6.31 (s, 1H), 6.17 (d, J=9.6, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.73 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.60, 159.92, 159.50, 158.77, 147.59, 138.85, 131.76, 130.01, 127.89, 124.52, 121.81, 114.10, 103.96, 103.26, 98.82, 98.49, 70.18, 55.78, 55.40, 55.31, 55.25.

*4.2.3. Preparation of {2,4-dimethoxy-6-[2-(4-methoxy-phenyl)--vinyl]-phenyl}-(3,5-dimethoxy-phenyl)-methanone (**1q**).* Solid $NaHCO_3$ (3.30 g, 39.4 mmol, 10 equiv) and Dess–Martin periodinane (1.67 g, 3.94 mmol, 1.0 equiv) were added sequentially in single portions to a solution of **1s** (1.72 g, 3.94 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at 25 °C, and the resultant slurry was stirred for 2 h at 25 °C. Upon completion, the reaction contents were quenched with saturated aqueous Na_2SO_3 (10 mL) followed by stirring the resultant biphasic system vigorously for 5 min at 25 °C. The reaction contents were then poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to afford the {2,4-dimethoxy-6-[2-(4-methoxy-phenyl)-vinyl]-phenyl}-(3,5-dimethoxy-phenyl)-methanone **1q** as a white solid.

Compound (**1q**): ^1H NMR (400 MHz, $CDCl_3$) δ: 7.27–7.25 (m, 2H), 7.00–6.97 (m, 3H), 6.84–6.72 (m, 4H), 6.63–6.62 (m, 1H), 6.41 (d, J=2.0, 1H), 3.89 (s, 3H), 3.78 (s, 6H), 3.76 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.22, 161.24, 160.71, 159.48, 158.28, 140.34, 137.65, 130.91, 129.54, 127.97, 122.97, 121.26, 113.93, 107.22, 105.55, 101.06, 97.62, 55.71, 55.45, 55.40, 55.17.

*4.2.4. Preparation of (±)-ε-viniferin (**1r**).* A solution of $FeC1_3 \cdot 6H_2O$ (1.24 g, 4.58 mmol) in water (8 mL) was added dropwise to a solution of resveratrol (1.03 g, 4.52 mmol) in methanol (10 mL) under stirring. The mixture was kept at room temperature for 49 h. After removal of the methanol in vacuum, the residue was diluted with water and extracted with EtOAc three times. Then the combined organic layer was evaporated to dryness, which was subjected to chromatography on silica gel column eluted with cyclohexane–acetone (3:1 to 2:1) to provide compound **1r** as gray

amorphous powder (310 mg, 30.2%) and unreacted resveratrol (408 mg) was recycled, respectively.

Compound (**1r**): ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.29 (br, 5H), 7.22–7.17 (m, 4H), 6.91 (d, J=16.0, 1H), 6.84 (d, J=8.4, 2H), 6.75–6.70 (m, 4H), 6.33 (d, J=1.6, 1H), 6.25 (s, 3H), 5.43 (d, J=5.6, 1H), 4.48 (d, J=5.6, 1H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 162.56, 159.93, 159.66, 158.27, 147.53, 136.52, 133.97, 130.18, 130.02, 128.81, 128.03, 123.58, 119.93, 116.39, 116.23, 107.08, 104.30, 102.17, 96.88, 94.00, 57.20.

Acknowledgements

We are grateful for the NSFC (No. 21072079), International Cooperation and Exchanges NSFC (No. 20921120404), and Research Fund for the Doctoral Program of Higher Education of China (No. 20100211120014) financial support.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.073.

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