An Efficient Microwave-Promoted Route to (*Z*)-Stilbenes from *trans*-Cinnamic Acids: Synthesis of Combretastatin A-4 and Analogues

Marc-Antoine Bazin,[a,1] Marie Jouanne,[a] Hussein El-Kashef,[b] Sylvain Rault*[a]

[a] Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), UPRES EA-4258, FR CNRS INC3M, Université de Caen Basse-Normandie, U.F.R. des Sciences Pharmaceutiques, Boulevard Becquerel, 14032 Caen Cedex, France
Fax +33(2)31931188; E-mail: sylvain.rault@unicaen.fr

[b] Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

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Abstract: *cis*-Stilbenes were synthesized from *trans*-cinnamic acids, involving ethylenic-bond bromination and a subsequent one-pot microwave-promoted stereoselective debrominative decarboxylation–Suzuki cross-coupling strategy. This sequence represents a useful way to prepare a variety of combretastatin A-4 derivatives.

Key words: *cis*-stilbenes, cinnamic acids, combretastatin A-4, debrominative decarboxylation, Suzuki–Miyaura cross-coupling reaction

Combretastatin A-4 (CA-4) is the most important *cis*-stilbene naturally occurring product isolated from the bark of the South African tree *Combretum caffrum* (Figure 1).[2] This compound strongly inhibits the polymerization of tubulin by interacting with the colchicine binding site on tubulin.[3] It possesses a highly potent antitumor activity.[2,4] Combretastatin A-4 in the form of a water-soluble phosphate prodrug (CA-4P, Figure 1), is currently in phase II and III clinical trials for the treatment of solid tumours.[5–7] Because of its simple structure, a large number of CA-4 analogues has been synthesized and evaluated in SAR studies.[8]

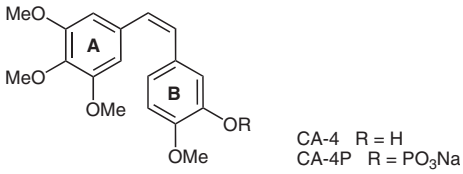


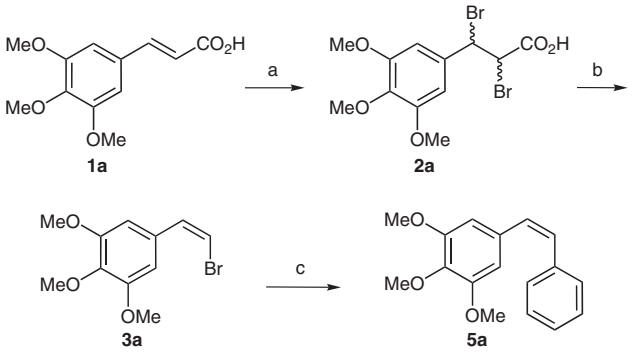
Figure 1 Combretastatin A-4 and its water-soluble phosphate prodrug CA-4P

Several methods have been reported for the synthesis of these compounds, based on the utility of these methods in giving access to a stereospecific *cis*-geometrical isomer. The most common ones are, the Wittig reaction between a phosphonium salt and an aromatic aldehyde,[9] and also the stereoselective reduction of diarylalkynes.[10] Moreover, the Suzuki cross-coupling reaction of *cis*-β-bromostyrenes gives a straightforward access to *cis*-stilbenes and provides a great molecular diversity due to the commercially available boronic acid building blocks.[3c,11] On the other hand, the *cis*-β-bromostyrene derivatives can be obtained by stereoselective reduction of β,β-dibromostyrenes using tributyltin hydride and tetrakis(triphenylphosphine)palladium(0)[12] or by the debrominative decarboxylation of an *anti*-2,3-dibromo-3-arylalkanoic acid.[13]

As a part of our ongoing program directed to the synthesis of stilbene derivatives, we have recently published an original one-pot microwave-promoted Hunsdiecker–Suzuki reaction for the synthesis of *trans*-stilbenes from *trans*-cinnamic acids.[14] The success of this methodology prompted us to transpose it for the synthesis of the other geometrical isomers *cis*-stilbenes.

Thus we wish to report herein a new strategy for the synthesis of some unknown *cis*-stilbenes, CA-4 analogues, from *trans*-cinnamic acids as depicted in Scheme 1.

Firstly, the *trans*-3,4,5-trimethoxycinnamic acid (**1a**), used as a starting material, was brominated[15] to give the corresponding 2,3-dibromo-3-(3,4,5-trimethoxyphenyl)propanoic acid (**2a**). The latter compound was subjected to stereoselective debrominative decarboxylation under microwave irradiation, following the procedure described by Kuang,[16] giving the *cis*-vinylbromide **3a** in a good yield. Compound **3a** was then allowed to react with phenylboronic acid **4a** via a Suzuki cross-coupling reaction to give the *cis*-stilbene **5a** (Scheme 1).



Scheme 1 *Reagents and conditions*: (a) Br_2, $CHCl_3$, r.t., 2 h, 82%; (b) Et_3N, DMF, 140 °C, MW, 1 min, 77%; (c) phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DME–H_2O (2:1), 100 °C, MW, 15 min, 80%.

The choice of the cinnamic acid **1a** as a starting material came in the light of the SAR studies of CA-4 derivatives which revealed that the trimethoxy substituents of ring A

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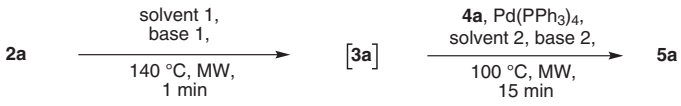
Table 1 Solvent Optimization for a One-Pot Reaction



Entry	Solvent 1	Base 1	Solvent 2	Base 2	Product
1	DME–H_2O (2:1)	K_2CO_3	DME–H_2O (2:1)	K_2CO_3	(*E*)-**5a**[a]
2	DMF	Et_3N	DMF	$K_3PO_4 \times H_2O$	–[b]
3	DMF	Et_3N	DME–H_2O (2:1)	K_2CO_3	(*Z*)-**5a** (64%)[c]

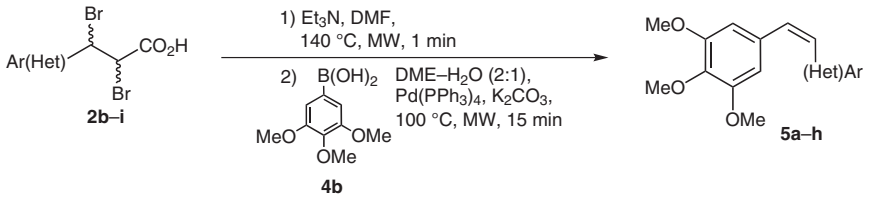
[a] Determined by ^1H NMR (400 MHz).
[b] Ill-defined products.
[c] Isolated yield (two steps from **2a**).

are essential for the activity, meanwhile ring B is amenable to substitutions.[17]

Second, we studied the possibility of carrying out the two reactions, the debrominative decarboxylation and the Suzuki cross-coupling reaction in a one-pot procedure in the same vial under microwave irradiation. This methodology has not been reported before. To the best of our knowledge, only a single paper has reported a one-pot synthesis involving a debrominative decarboxylation and a Pd-catalyzed Sonogashira cross-coupling reaction.[16]

The attempted trials of our study are depicted in Table 1. Thus, when a single solvent was used for both reactions, the attempted reaction failed to give the target product (entries 1 and 2). Treatment of **2a** with K_2CO_3 in DME–H_2O (2:1) gave the *trans*-isomer of **5a**, while using DMF as a solvent and $K_3PO_4 \cdot H_2O$ as a base in the second step,[18] the one-pot reaction gave ill-defined products. These failures urged us to choose standard conditions for each step. Thus, when DMF was kept to a minimum in the first step, and then when Suzuki cross-coupling reagents were added in a large volume of the solvent DME–H_2O (2:1) in the second step, the target *cis*-stilbene **5a** was successfully obtained in a good yield (64%, entry 3). This result confirms the mechanism proposed by Kuang[13] for debrominative decarboxylation by *trans*-β-elimination in the first step of our reaction when DMF–Et_3N was used leading to a *cis*-bromostyrene. On the other hand, probably a unimolecular elimination process occurred when DME–H_2O and K_2CO_3 were employed leading to a *trans*-isomer.

Table 2 Synthesis of CA-4 Derivatives



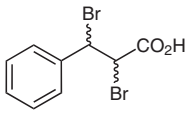
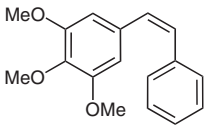
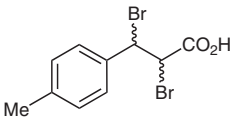
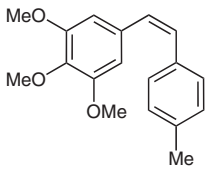
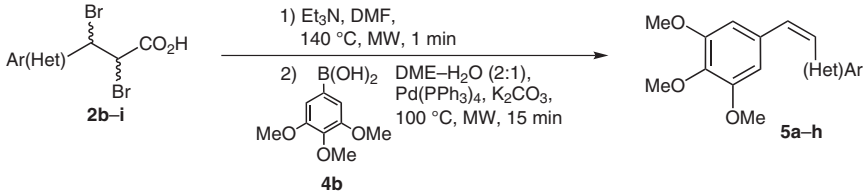
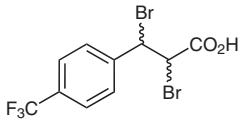
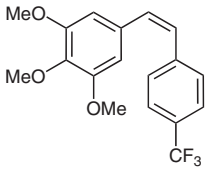
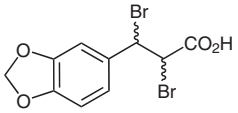
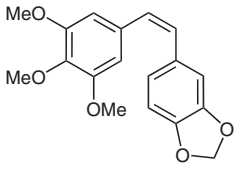
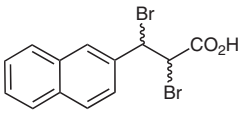
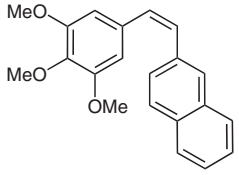
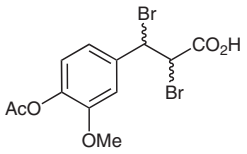
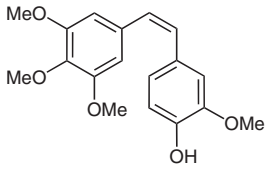
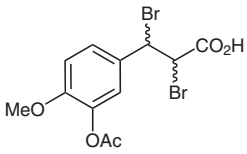
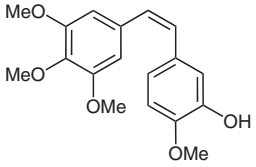
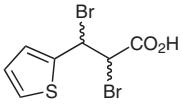
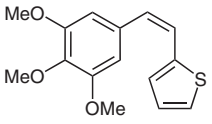
Entry	Substrate	Product	*Z*/*E* ratio[a]	Yield (%)[b]
1	 **2b**	 **5a**	80:20	76
2	 **2c**	 **5b**	90:10	52

Table 2 Synthesis of CA-4 Derivatives (continued)



Entry	Substrate	Product	*Z*/*E* ratio[a]	Yield (%)[b]
3	 **2d**	 **5c**	>95:5	46
4	 **2e**	 **5d**	90:10	53
5	 **2f**	 **5e**	85:15	63
6	 **2g**	 **5f**	60:40	42[c]
7	 **2h**	 **5g**	75:25	41[c]
8	 **2i**	 **5h**	80:20	21

[a] Determined by ^{1}H NMR.
[b] Isolated yield (two steps from **2**).
[c] NaOH was used as base.

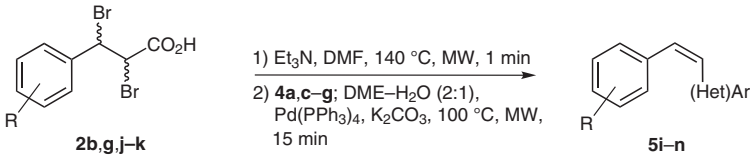
For a typical one-pot microwave-promoted debrominative decarboxylation–Suzuki cross-coupling procedure,[19] Et_3N was added to 2,3-dibromoalkanoic acids **2** in DMF (1 mL) in a 10 mL vial. After completion of the debrominative decarboxylation reaction (microwave heating, 140 °C, 1 min), Suzuki cross-coupling reagents were added: the boronic acid, K_2CO_3 or NaOH, $Pd(PPh_3)_4$, and DME–H_2O (2:1, 8 mL). Then microwave heating was restarted for 15 minutes at 100 °C. This short-time procedure allowed the synthesis of various trimethoxystilbenes in good yield.

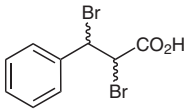
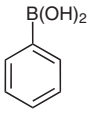
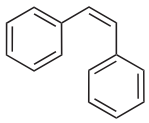
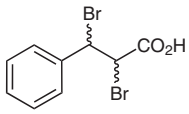
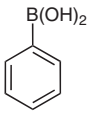
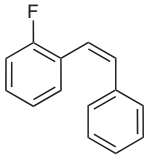
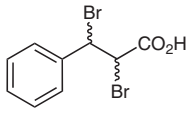
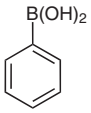
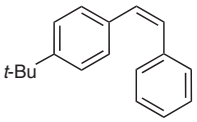
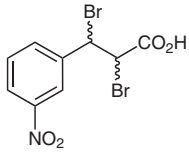
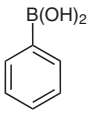
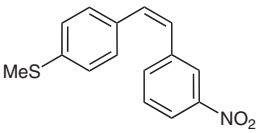
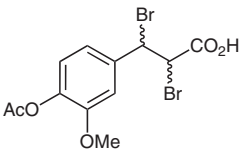
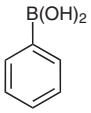
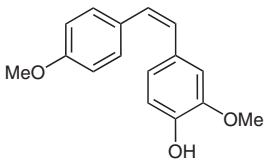
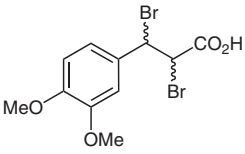
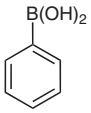
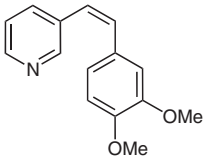
It is noteworthy that the *cis*-stilbene **5a** could be obtained alternatively by the same one-pot methodology, starting

from *trans*-cinnamic acid and using 3,4,5-trimethoxyphenylboronic acid as a coupling agent in the Suzuki cross-coupling reaction. To investigate the scope of this protocol, a variety of CA-4 analogues **5a**–**h** was synthesized using different *anti*-2,3-dibromoalkanoic acids, readily available from *trans*-α,β-unsaturated carboxylic acids, and the same trimethoxyphenylboronic acid (Table 2). The use of the latter boronic acid fulfills the criterion of the biological activity due to the presence of the three methoxy groups of ring A and provides a cheaper reaction.

As we mentioned above the *Z*/*E* stereoselectivity is first governed by debrominative decarboxylation reaction conditions. In agreement with the literature,[13] *anti*-2,3-dibromo-3-arylpropanoic acids carrying electron-withdrawing groups (e.g., 4-trifluoromethyl, entry 3) gave high *Z*/*E* ratios. On the contrary, the *Z*/*E* stereoselectivity was reduced when the aromatic ring was substituted with electron-donating groups (entries 2 and 4). This is why CA-4 (**5g**) and iso-CA-4 (**5f**) were obtained in moderate yields (41% and 42%, respectively). This methodology

Table 3 Synthesis of Substituted (*Z*)-Stilbenes



Entry	*anti*-2,3-Dibromo-3-phenylpropanoic acid	Boronic acid	Product	*Z*/*E* ratio[a]	Yield (%)[b]
1	 **2b**	 **4a**	 **5i**	95:5	61
2	 **2b**	 **4c**	 **5j**	95:5	52
3	 **2b**	 **4d**	 **5k**	95:5	86
4	 **2j**	 **4e**	 **5l**	80:20	43
5	 **2g**	 **4f**	 **5m**	60:40	28[c]
6	 **2k**	 **4g**	 **5n**	80:20	36

[a] Determined by ^{1}H NMR (400 MHz).
[b] Isolated yield (two steps from **2**).
[c] NaOH was used as base.

also allowed the synthesis of original *cis*-stilbenes such as the thiophene derivative **5h** in an acceptable yield.

In each case, the *Z*/*E* ratio was determined by ^{1}H NMR, and it was possible to isolate the pure *Z*-isomers using silica gel column chromatography.

Finally, for the sake of evaluating the scope and limitations of this methodology, a series of various substituted (*Z*)-stilbenes was synthesized. The results are presented in Table 3.

The reaction sequence provided different results depending on the substitution of the phenyl ring of the arylpropanoic acid **2**. Unsubstituted acids (entries 1–3) gave good yields and excellent *Z*/*E* ratios (ca. 95:5). The presence of electron-withdrawing (entry 4) or electron-donating (entry 6) groups lead to a loss of the stereoselectivity and yield. In the case of the nitro derivative (entry 4), the decrease of both yield and selectivity is probably due to a loss of reactivity during the Suzuki step since the first step afforded the (*Z*)-β-bromostyrene in a high stereoselectivity as reported.[13,16]

In conclusion, we have developed a new and efficient microwave-promoted synthesis of *cis*-stilbenes, CA-4 analogues, using *trans*-cinnamic acids as starting materials. The scope and limitations of this new methodology has been studied. Our procedure proved to be very useful to prepare a library of CA-4 analogues whose biological evaluation is in progress.

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References and Notes

(1) Current address: Université de Nantes, Nantes Atlantique Universités, IICiMed EA1155, UFR des Sciences Pharmaceutiques, Laboratoire de Chimie Thérapeutique, 1 Rue Gaston Veil, BP 53508, 44000 Nantes, France.

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(19) **General Procedure for the One-Pot Synthesis of 5a–n**
In a 10 mL microwave vial were introduced a magnetic stir

bar, a *anti*-2,3-dibromo-3-arylpropanoic acid **2** (5.0 mmol, 1.00 equiv), and Et_3N (1.05 equiv) in DMF (1 mL). The vial was sealed, and the suspension was then heated at 140 °C for 1 min. After CO_2 removal were added a boronic acid **4** (1.20 equiv), K_2CO_3 (2.50 equiv) or NaOH (3.50 equiv), $Pd(PPh_3)_4$ (0.05 equiv), and DME–H_2O (2:1, 8 mL). The vial was sealed and purged with argon through the septum inlet. The suspension was then heated at 100 °C for 15 min. The resulting mixture was acidified with 1 N HCl. H_2O and Et_2O were added, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and evaporated. The crude product was then purified by silica gel chromatography (eluent: cyclohexane–EtOAc) to afford (*Z*)-stilbene **5** as a pure compound. Compound *trans*-**5** was isolated too, to determine the *Z*/*E* ratio.

Selected Data

Compound **5d**: orange solid; yield 0.51 g (63%); mp 78 °C. IR (KBr): ν = 2931, 2831, 1581, 1510, 1487, 1454, 1330, 1235, 1129, 1024, 1006, 846 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.71 (s, 6 H, 2 × OMe), 3.85 (s, 3 H, OMe), 5.92 (s, 2 H, OCH_2O), 6.42 (d, *J* = 11.7 Hz, 1 H, =CH), 6.48 (d, *J* = 11.7 Hz, 1 H, =CH), 6.51 (s, 2 H, H_{ar}), 6.73 (d, *J* = 8.8 Hz, 1 H, H_{ar}), 6.79–6.81 (m, 2 H, H_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9 (2 C, 2 × OMe), 60.9 (OMe), 100.9, 105.9 (2 C), 108.1, 109.0, 122.9, 129.1, 129.4, 131.1, 132.5, 137.1, 146.6, 147.3, 152.9 (2 C). ESI-MS: *m/z* = 315 $[M + H]^+$. HRMS (EI): *m/z* calcd for $C_{18}H_{18}O_5$: 314.1154; found: 314.1165.

Compound **5m**: yellow solid; yield 0.17 g (45%); mp 58 °C. IR (KBr): ν = 3417, 2956, 1605, 1511, 1465, 1274, 1241, 1175, 1029, 870 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 5.58 (s, 1 H, OH), 6.42 (part A of AB system, $^3J_{AB}$ = 11.7 Hz, 1 H, =CH), 6.45 (part B of AB system, $^3J_{AB}$ = 11.7 Hz, 1 H, =CH), 6.77–6.79 (m, 5 H, H_{ar}), 7.22 (d, *J* = 8.8 Hz, 1 H, H_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (OMe), 55.7 (OMe), 111.1, 113.5, 114.1, 122.4, 126.1, 127.4, 128.3, 128.7, 130.1, 144.7, 146.0, 158.5. ESI-MS: *m/z* = 257 $[M + H]^+$. HRMS (EI): *m/z* calcd for $C_{16}H_{16}O_3$: 256.1099; found: 256.1109.