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Tandem Heck–Suzuki–Miyaura reaction: Application to the synthesis of constrained analogues of combretastatin A-4

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Abstract—A series of compounds related to combretastatin A-4 has been synthesized by a tandem Heck-carbocyclization/Suzuki coupling process. From various alkynamides and 3,4,5-trimethoxyphenyl boronic acid or the corresponding styryl derivative, (*E*)-3-arylmethyleneoxindoles (type **I**) and (*EE*)-3-alkylideneoxindoles (type **II**) were efficiently obtained in a stereoselective manner. Factors influencing yield and stereoselectivity are detailed.

Combretastatin A-4 (CA4) is a naturally occurring stilbene isolated from *Combretum caffrum*. This compound, which strongly inhibits the polymerization of tubulin by binding to the colchicine site, has been shown to selectively target the vascular system of tumours. For these tumour blood vessels, it ensues a rapid and irreversible vascular shutdown leading to extensive ischemic necrosis of the tumour cells.[1] A key structural factor for potent biological activity is the presence of the cis-double bond, or of a suitable linker, forcing the two aromatic rings to be within an appropriate distance.[2] Recently, we reported the stereospecific synthesis of vinylogous CA4 analogues, the two geometric isomers **1** and **2**, and derivative **3** with a phenyl group as the B-ring.[3] Diene **3** was found to be a more potent inhibitor of tubulin polymerization than CA4, although displaying a poor cytotoxicity. Therefore, compound **3** appears to be an interesting lead compound for the search of specific and potent antivascular agents (Fig. 1).

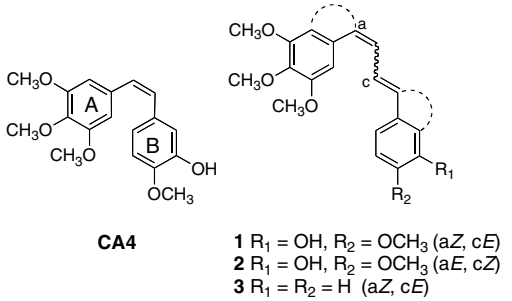
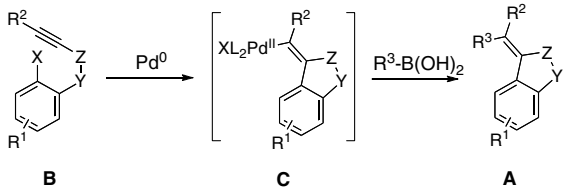


Figure 1. Structure of CA4, its vinylogous analogues and their considered constrained derivatives.

In view of reducing the conformational flexibility associated with the two phenyl rings of CA4 and diene **3**, structures incorporating another ring between the cis-double bond and one of the aromatic substituent were considered. Access (Scheme 1) to such conformationally restricted derivatives of type **A** with carbo or heterocycles fused with one of the aromatic rings could be conceivable stereoselectively, by a tandem Heck–Suzuki coupling process starting from alkyne tethered halogenoarenes of type **B** and boronic acids.[4–10] This reaction sequence involves an intramolecular carbopalladation of alkynes **B** in a *syn* fashion (5-*exo*-*dig* cyclization) followed by cross-coupling of the (*E*)-vinylpalladium



Scheme 1. Palladium catalyzed formation of type **A**-compounds.

Keywords: Combretastatin A4; Oxindole; Domino reaction; Palladium catalysis.
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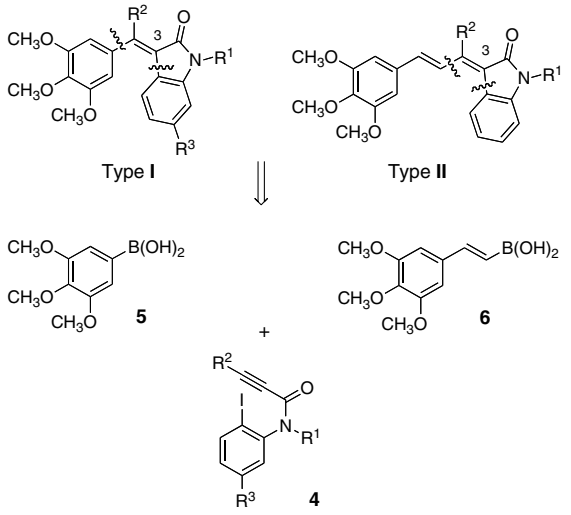


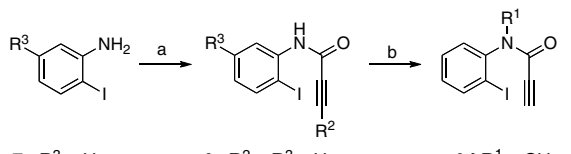
Scheme 2. Synthetic strategy for oxindole derivatives **I** and **II**.

intermediates **C** with boronic acids, proceeding with a retention of the olefinic configuration.[11]

Stereoselective syntheses of carbo- or heterocyclic rings bearing a substituted exocyclic olefin group have been reported via this palladium catalyzed domino approach: indanes,[5,6] indoles,[4] indolinones[8,9] or isoindolinones.[7]

For our purpose, we first planned to synthesize derivatives with a lactam cycle fused to the B-ring, the (*E*)-3-arylmethyleneoxindoles (type **I**) and the (*EE*)-3-alkylideneoxindoles (type **II**), that are considered as conformationally restricted analogues of CA4 and dienes **1**–**3**, respectively (Scheme 2).[12] This convergent approach involved coupling of the suitable cyclization precursors, the alkynamides of type **4**, with the commercially available trimethoxyphenyl boronic acid **5** or the corresponding styryl derivative **6**.[3]

To investigate the feasibility of this tandem process, several alkynamides **4** were prepared from the 2-iodoaniline **7a** (Scheme 3).[13] Thus, coupling with propynoic **8a** or but-2-ynoic acid **8b** using DCC afforded the corresponding anilides **4a** and **4b** in, respectively, 58% and 52% yield.[14] The *N*-alkylamides **4d** ($R^1 = CH_3$) and **4e** ($R^1 = Bn$) were prepared in good yields by reaction of 2-iodopropynamide **4a** with, respectively, methyl iodide or benzyl bromide using sodium hydride as the base. In order to set out the desired oxindole products (types **I** and **II**) with a free NH function, a removable protecting group of the alkynamide was required and the SEM group was chosen. The N-SEM derivative **4f** was obtained using the same alkylation process.



Scheme 3. Synthesis of alkynamides **4a**–**f**. Reagents and conditions: (a) R^2-C≡CCO_2H **8a** or **8b**, DCC, CH_2Cl_2, 0 °C to rt 36–58%; (b) from **4a**, (i) NaH, THF, 0 °C, (ii) R^1X, rt 68–82% (0.1 equiv tetrabutylammonium bromide was added for **4e**).

Anilide **4c** bearing a methoxy group was prepared by coupling iodoanisidine **7b** ($R^3 = OMe$)[15] with but-2-ynoic acid under the usual conditions (36% yield).

All the tandem reactions studied were conducted in dry THF at 60 °C in the presence of 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 1.1 equiv of the aryl- or vinylboronic acids **5** or **6** (Table 1). Two bases were investigated, CsF (3 equiv)[9] or aqueous NaOH (1.5 equiv).[7] We initially attempted the reaction of *N*-free alkynamide **4a** with arylboronic acid **5** in the presence of CsF (entry 1). Propynamide **4a** was completely consumed within 2 h but failed to undergo the cascade reaction.

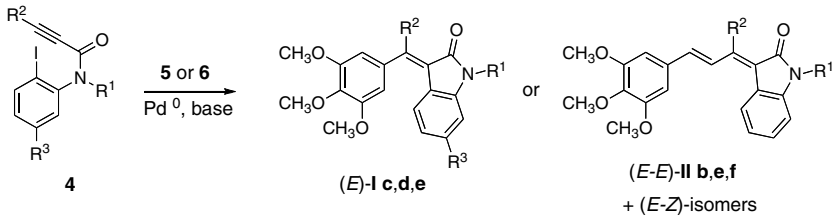
Then, we considered coupling reactions with *N*-alkylamides. With the *N*-methyl substrate **4d** (entry 2) a complete transformation occurred within 3 h, and the desired 3-arylidene product **Id** was formed as a single stereoisomer albeit in low yield (20%). Reaction with the *N*-benzyl alkynamide **4e** provided alkene **Ie** in increased yield (50%) and with the same high stereoselectivity (entry 3). Presumably, the efficiency of the cascade reaction was dependent on conformational aspects of the starting alkynamides. When the amido group was alkylated with a bulkier substituent, for example, Bn versus Me, favourable steric interactions provided a higher population of the correct rotamer that could then undergo the carbopalladation step.[13,14]

Being a viable substrate for the tandem reaction, benzylamide **4e** was also treated with the vinyl boronic acid **6** (entry 4). The corresponding 3-alkylideneoxindole **IIe** was obtained in acceptable yield (50%) and good selectivity (*EE*/*EZ* = 97:3). With both boronic acids, the cascade reactions proceeded with the same stereoselectivity when aqueous NaOH was used as a base (entries 5 and 6). Nevertheless, alkene **Ie** was obtained in a slightly diminished yield (30%) and with a longer reaction time.

With the *N*-SEM alkynamide **4f**, a significant enhancement of the reaction rate was observed (entries 7 and 8). When NaOH was used as a base, cycloadduct **IIf** was obtained in 90% yield but as a mixture of the two stereoisomers (*EE*/*EZ* = 6:4), whereas, in the presence of CsF, this diene was produced in 68% yield as a single isomer (*EE*).

Although the desired *E*-isomers of the synthesized oxindole products **Id**,**e** and **IIe**,**f** were obtained in pure form after silica gel chromatography, they are prone to isomerization under the influence of light or in protic media.[16] Nevertheless, it is conceivable that substitution of the olefinic proton (R^2) with a small alkyl group, such as a methyl group, could stabilize the *E*-configuration of the exocyclic double bond, without altering their biological activity.[17,18] Moreover, it is noteworthy that the

Table 1. Palladium catalyzed tandem reactions of various alkynamides **4** with boronic acids **5** or **6**[a]



Entry	Alkyne-amide	R_1	R_2	R_3	Boronic acid	Base	Time	Ratio[b] *E*/*Z*	Global yield[c] (%)	Product
1	**4a**	H	H	H	**5**	CsF	2 h	—	—	**Ia**
2	**4d**	CH_3	H	H	**5**	CsF	3 h	*E*	20	**Id**
3	**4e**	Bn	H	H	**5**	CsF	1 h	*E*	50	**Ie**
4	**4e**	Bn	H	H	**6**	CsF	2 h	97/3	55	**IIe**
5	**4e**	Bn	H	H	**5**	NaOH	4 h	*E*	30	**Ie**
6	**4e**	Bn	H	H	**6**	NaOH	2 h	96/4	50	**IIe**
7	**4f**	SEM	H	H	**6**	NaOH	0.5 h	6/4	90	**IIf**
8	**4f**	SEM	H	H	**6**	CsF	0.5 h	*E*	68	**IIf**
9	**4b**	H	CH_3	H	**6**	CsF	2 h	*E*	70	**IIb**
10	**4b**	H	CH_3	H	**6**	NaOH	0.25 h	2/8	70	**IIb**
11	**4c**	H	CH_3	OMe	**5**	CsF	3 h	*E*	80	**Ic**

[a] All reactions were performed with alkynamide **4** (1 equiv), boronic acid **5** or **6** (1.1 equiv), 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, CsF (3 equiv) or 2 N aqueous NaOH (1.5 equiv) in refluxing THF.[19]

[b] *E*/*Z* stereochemistry refers to the newly formed double bond. Ratio was determined by ^1H NMR analysis of the crude product.

[c] Isolated yield after column chromatography.

tandem reaction can be considered with a N-free alkynamide when the terminal end of the triple bond is substituted.[8,9] Indeed, when the reactions were performed with the N-free butynamide **4b** and vinylboronic acid **6**, in both reaction conditions, diene **IIb** was produced, in 70% yield (entries 9 and 10). As previously observed, cycloadduct **IIb** was obtained as a single isomer using CsF. In the presence of NaOH, a complete transformation occurred within 15 min, however leading to both isomers (ratio *EE*/*EZ* = 2:8). Surprisingly, the major product appeared to be the (*EZ*)-isomer. Results of runs 7–10 confirmed that CsF was a better additive than NaOH in our tandem process.

Finally, the reaction was attempted, in the presence of CsF, with arylboronic acid **5** and anilide **4c** bearing a 5-methoxy group (entry 11). Reaction outcome was not affected, and the desired constrained CA4 analogue **Ic** was obtained in good yield (80%) as a single isomer. As expected, methyl derivatives **Ic** and **IIb** proved to be of great stability.

The configuration (*E*) or (*Z*) of the newly formed double bond within this series of oxindole derivatives could be assigned based on the chemical shifts of particular protons:[9,20,21] H-vinylic and H-2′/H-6′ protons for derivatives **Id** and **Ie**, olefinic protons H-b and H-c for compounds **IIe** and **IIf**. Therefore, due to the anisotropic effect of the carbonyl group, proton H-c for the (*EE*)-isomer of derivative **IIe** appeared at a lower field than the corresponding signal for the (*EZ*)-isomer, whereas proton H-b appeared at a lower field for the (*EZ*)-isomer. Stereochemistry was unambiguously supported by NOESY experiments (Fig. 2). For both compounds bearing a methyl group on the exocyclic olefin (**Ic** and **IIb**), the configuration was also confirmed by chemical shifts (H-2′/H-6′ protons and H-b, respectively) and NOESY experiments.[22] For derivatives **IIb**,**e**,**f** a large coupling constant between H-a and H-b (14.5–16.0 Hz) confirmed the (*E*)-geometry of the introduced double bond.

In summary, the tandem Heck–Suzuki–Miyaura approach has proven to be a practical means for preparing 3-arylmethylene (type **I**) and 3-arylallylidene (type **II**) oxindoles. In both series, high stereocontrol was obtained by using CsF as an additive. We have shown that the trimethoxyphenyl boronic acid **5** and the corresponding vinyl derivative **6** are suitable coupling partners for this tandem reaction. It is noteworthy that the substitution (e.g. by a methyl group) of the newly formed double-bond stabilizes these oxindole derivatives. Compounds **Ic**,**d**,**e** and **IIb**,**e**,**f**, which are considered as new CA4 analogues are currently under

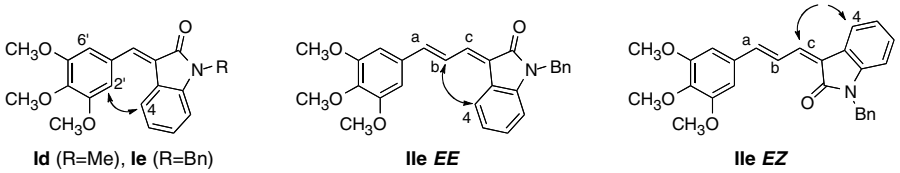


Figure 2. Configuration determination using NOESY experiments.

biological evaluation. Expansion of this work to the synthesis of derivatives with other heterocyclic cores is in progress.

Acknowledgements

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19. *Representative experimental procedure: synthesis of 1-benzyl-3-[3-(3′,4′,5′-trimethoxyphenyl)allylidene]indolin-2-one IIe (entry 4):* To a stirred solution of alkyneamide **4e** (80 mg, 0.221 mmol) in dry THF (12 mL) were added (*E*)-2-(3′,4′,5′-trimethoxyphenyl)vinylboronic acid **6** (58 mg, 0.243 mmol) and CsF (100 mg, 0.663 mmol). The resulting mixture was degassed (argon bubbling, 15 min) then PPh_3 (5.8 mg, 0.022 mmol) and $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) were added. After heating at reflux for 2 h, the reaction was cooled to rt, quenched with distilled water and extracted with diethylether (twice). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc: 8/2) to give successively (*EZ*)-**IIe** as an orange oil (2 mg) and (*EE*)-**IIe** (52 mg) as a pale orange crystalline solid (global yield: 55%) (*EZ*)-**IIe**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, $J = 15.6$, 11.5 Hz, 1H, H-b), 7.46 (d, $J = 7.4$ Hz, 1H, H-4), 7.33 (d, $J = 11.5$ Hz, 1H, H-c), 7.32–7.26 (m, 5H, H-Ph), 7.14 (td, $J = 7.6$, 1.0 Hz, 1H, H-6), 7.00 (td, $J = 7.6$, 1.0 Hz, 1H, H-5), 6.97 (d, $J = 15.6$ Hz, 1H), 6.83 (s, 2H, H-2′,6′), 6.70 (d, $J = 7.6$ Hz, 1H, H-7), 4.98 (s, 2H, CH_2), 3.91 (s, 6H, $OCH_3 \times 2$), 3.88 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5 (C), 153.4 (C × 2), 143.3 (CH-a), 141.6 (C), 139.5 (C), 136.4 (CH-c), 136.2 (C), 132.0 (C), 128.7 (CH × 2), 128.6 (CH), 127.5 (CH), 127.2 (CH × 2), 124.0 (CH-b), 123.9 (C), 123.5 (C), 121.9 (CH), 119.2 (CH), 108.9 (CH), 104.9 (CH × 2), 61.0 (CH_3), 56.2 ($CH_3 \times 2$), 43.3 (CH_2); ESI$^+$-MS: $m/z = 428$ $[M+H]^+$, 450 $[M+Na]^+$, 466 $[M+K]^+$. (*EE*)-**IIe**: orange crystals, mp 195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, $J = 7.6$ Hz, 1H, H-4), 7.58–7.47 (m, 2H, H-b, H-c), 7.32–7.26 (m, 5H, H-Ph), 7.17 (td, $J = 7.6$, 1.4 Hz, 1H, H-6); 7.10 (d, $J = 14.5$, 1H, H-a), 7.05 (td, $J = 7.6$, 1.0 Hz, H-5), 6.80 (s, 2H, H-2′,6′), 6.74 (d, $J = 7.6$ Hz, 1H, H-7), 4.98 (s, 2H, CH_2), 3.94 (s, 6H, $OCH_3 \times 2$), 3.90 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (C), 153.5 (C × 2), 144.4 (CH-a), 142.7 (C), 139.9 (C), 136.1 (CH-c), 136.0 (C), 131.7 (C), 128.8 (CH), 128.7 (CH × 2), 127.5 (CH), 127.2 (CH × 2), 124.8 (C), 123.2 (CH), 122.8 (CH-b), 122.5 (C), 122.0 (CH), 109.2 (CH), 104.9 (CH × 2), 61.0 (CH_3), 56.3 ($CH_3 \times 2$), 43.7 (CH_2). HRMS (DCI-NH_3): m/z calcd for $C_{27}H_{26}O_4N$ $[M+H]^+$: 428.1862; found: 428.1852.
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