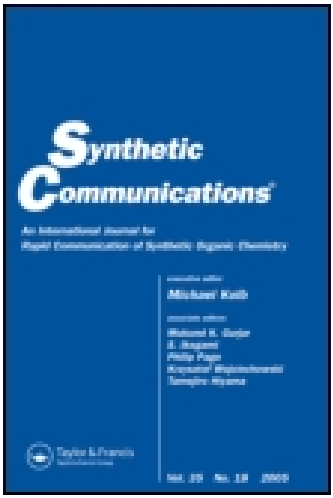

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Kumada-Corriu Cross Coupling Route to the Anti-Cancer Agent Combretastatin A-4

Alejandro A. Camacho-Dávila [a]
[a] Facultad de Ciencias Químicas, Universidad Autónoma de Chihuahua , Chihuahua, México
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Kumada–Corriu Cross Coupling Route to the Anti-Cancer Agent Combretastatin A-4

Alejandro A. Camacho-Dávila
Facultad de Ciencias Químicas, Universidad Autónoma de Chihuahua, Chihuahua, México

Abstract: A short and efficient synthesis of the anticancer agent combretastatin A-4 was accomplished from inexpensive starting materials using the iron-catalyzed cross-coupling of a Grignard reagent and a bromostilbene as the key step.

Keywords: Anticancer, cross-coupling, iron catalysis, stilbene

Combretastatin A-4 (CA-4) (Figure 1) **1** is the most active member of a group of naturally occurring stilbenes isolated from the african shrub *Combretum caffrum* by Pettit et al.[1] Despite its simple structure, CA-4 has showed marked biological activity and interacts strongly with the colchicine site on tubulin. Pronounced cytotoxic activity against several cancer cell lines such L1210 lymphocytic leukaemia cells and the P388 murine leukemia cell line in the μM range has been demonstrated.[2] Vasculature inhibition of solid tumors by CA-4 has also been demonstrated.[3]

Structure–activity studies have shown that the *E* isomer of **1** and analogs show a much lower activity, therefore to access the biologically active *Z* isomers stereoselective synthetic routes are required.[4] Also, the presence of the 3,4,5-trimethoxybenzene substitution in ring A is crucial to biological activity. Studies have also shown that ring B can be modified to a larger extent to yield potent analogs.[5] Some of these are presented in Fig. 2. The water-soluble phosphate **4** is actually under

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Address correspondence to Alejandro A. Camacho-Dávila, Apartado Postal 1542-C, Chihuahua, Chih. 31170, México. E-mail: acamach@uach.mx

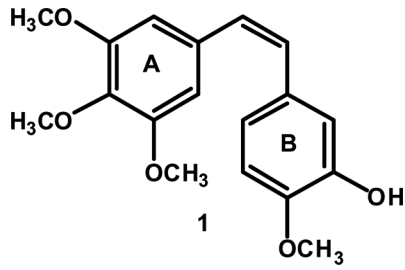


Figure 1. Structure of combretastatin A-4.

clinical trials as vascular tumor targeting agent.[6] All of these properties coupled with its simple structure have encouraged the synthetic efforts toward CA-4 and its analogs, and several syntheses have been reported.[7]

Synthetic routes based on the Wittig reaction,[1,8] Perkin condensation,[9] Suzuki cross coupling,[10] Sonogashira cross-coupling,[3,11] and Ramber–Backlund reaction[12] have all been reported. Some of these reactions suffer either from poor stereocontrol of the double-bond geometry or low yield and are therefore difficult to carry out on a preparative scale.

A very useful reaction for the stereoselective synthesis of *Z* or *E* stilbenes is the Kumada–Corriu cross-coupling reaction, which involves the coupling of aryl or vinylmagnesium organometallics **A** and vinyl or aryl halides **B** by the use of catalysts derived from palladium, nickel, or iron to

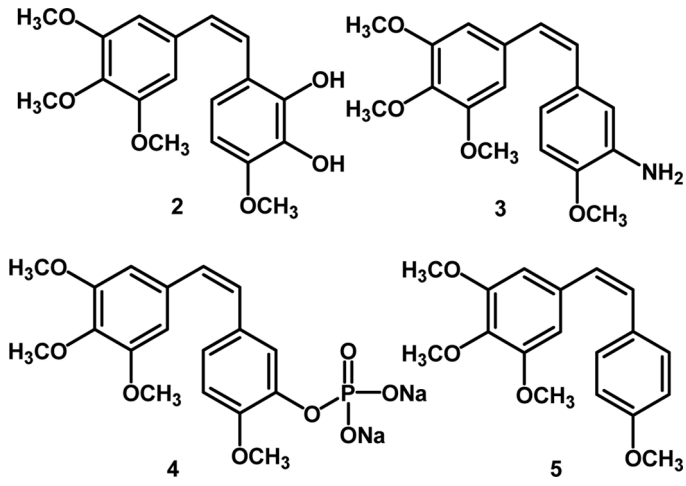
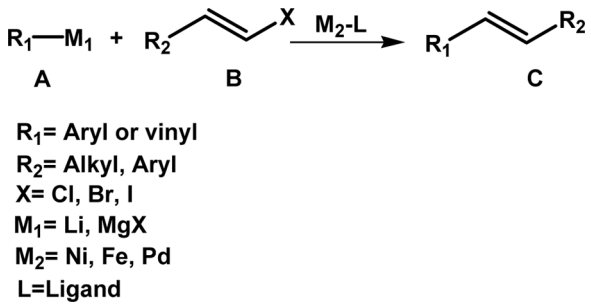


Figure 2. Structure of combretastatin A-4 analogs.

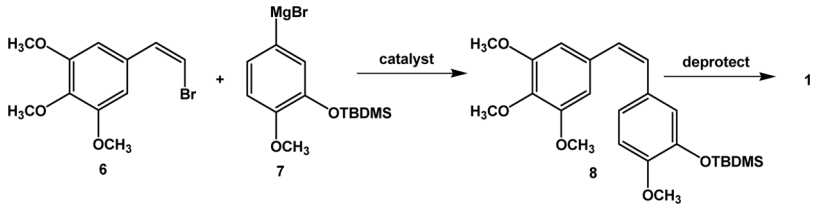


Scheme 1.

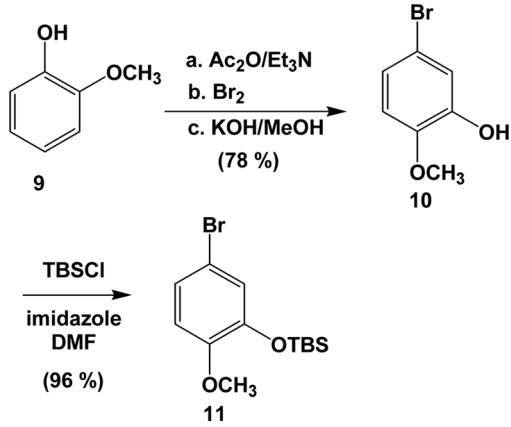
obtain cross-coupling products of type **C** in good yields with retention of the double-bond configuration (Scheme 1).[13,14] Previous reports on the Kumada–Corriu cross-coupling between the aryl and vinyl compounds shows that this reaction take place more effectively when the organometallic part is on the aryl side rather than on the vinyl side.[14a]

The biological importance of combretastatins and specifically of CA-4 **1** prompted us to explore a practical synthesis of **1** using a metal-catalyzed cross-coupling between *Z* vinyl bromide **6** and arylmagnesium bromide **7** (Scheme 2). There are no previous reports on the synthesis of combretastatin A-4 or its analogs using the Kumada–Corriu cross-coupling, although this reaction has been used on several occasions in the synthesis of other stilbenes, mainly through the use of palladium catalysts.[15]

The synthesis of combretastatin A-4 therefore started with the synthesis of 5-bromo-2-methoxyphenol **10** prepared via treatment of the inexpensive guaiacol **9** with acetic anhydride and triethylamine, followed by bromination of the resulting acetate. Saponification using potassium hydroxide in methanol afforded **10** in 78% yield over three steps.[16] The phenolic function was then protected in almost quantitative yield as the TBDMS ether **11** by reaction of **10** with *tert*-butyldimethylchlorosilane and imidazole in DMF as solvent (Scheme 3).[17]



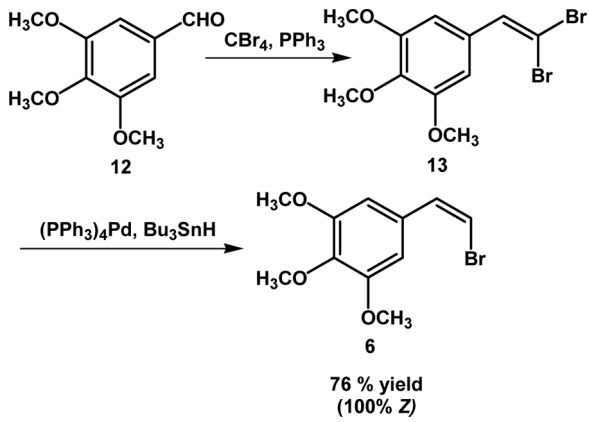
Scheme 2.



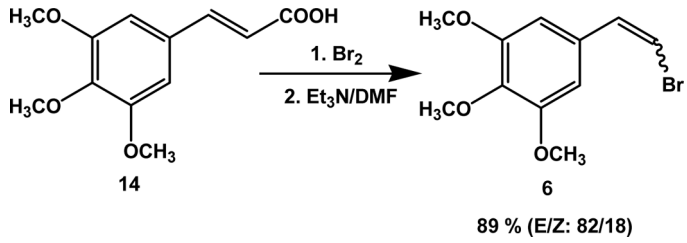
Scheme 3.

Next, the synthesis of *Z*-bromostyrene **6** was investigated. Stereoisomerically pure 3,4,5-trimethoxy-(*Z*)-β-bromostyrene **6** has been previously obtained stereoselectively by the Corey–Fuchs reaction between aldehyde **12** and carbon tetrabromide to afford 3,4,5-trimethoxydibromostyrene **13**. Palladium-catalyzed reduction of **13** with tributyltin hydride provided (*Z*)-bromide **6** in 76% yield as the exclusive isomer (Scheme 4).[18]

The main drawback of this procedure that precludes its use in a practical synthesis of **1** is the use of highly toxic tin compounds and the poor atom economy. The problems associated with this method prompted us



Scheme 4.



Scheme 5.

to explore an alternate route to this compound. To this end, the dehydrohalodecarboxylation of dibromocinnamic acids, a reaction that provides *Z*-bromostyrenes stereoselectively and in good yield, was explored.[19] Base-induced dehydrobromodecarboxylation of 3,4,5-trimethoxydibromocinnamic (obtained by bromination of the commercially available 3,4,5-trimethoxycinnamic acid **14**) was accomplished with triethylamine in DMF according to the reported procedure[19] to afford bromostyrene **6** in 89% yield (Scheme 5). The proton NMR of the product showed it to be an inseparable mixture of *E* and *Z* isomers in a ratio of 82:18. This result agrees with the previously reported procedure where the debromodecarboxylation of **15** was carried out with triethylamine using microwaves.[20] The cause for this reduction on the *Z*-isomer formation selectivity may derive from the presence of the electron-donating groups on the aromatic ring causing a reduction on the stereospecificity of the bromine addition. It is well known that during the addition of bromine to electron-rich aromatic systems, the stabilization of the positive charge is more important than the formation of a cyclic bromonium ion. This result in a reduction on the *erythro/threo* stereoselectivity of the dibromo addition product, which is reflected on the dehalodecarboxylation product.[21]

Although this sequence affords a mixture of isomers, the predominance of the required *Z* isomer and the use of inexpensive starting materials allows for the large-scale preparation of **1** if coupling of vinyl bromide **6** with the protected Grignard reagent **7** proceeds stereoselectively and in high yield. To this end, the metal-catalyzed cross-coupling reaction using the mixture of isomers of **6** and Grignard reagent **7** was examined.

Cahiez and Knochel have reported the iron(III)-catalyzed cross-coupling reaction between arylmagnesium halides and alkenyl halides using the inexpensive ferric acetylacetonate as catalyst. This reaction afforded the corresponding coupling products with retention of stereochemistry of the double bond.[22] It was very pleasing to find that the

coupling of protected Grignard reagent **7** (1.25 equivalents) and vinyl bromide **6** in the presence of 5 mol% of iron(III) acetylacetonate at 0°C in THF proceeded in a favorable way. Column chromatography of the reaction product afforded in elution order the dimethoxybiphenyl TBS ether resulting from the homo coupling of Grignard reagent **7** in 10–12% yield, followed by pure *Z* combretastatin A-4 TBDMS ether isomer **8** in 61% yield, then a mixture of *Z*/*E* isomers of TBDMS ether of combretastatin, and finally, some unreacted vinyl halide (the *Z*/*E* isomer ratio of this product was not analyzed). Increasing the catalyst load to 10 mol% did not improve the yield of cross-coupling product but caused an increase in the Grignard homocoupling product (25–30%). Finally, deprotection of pure *Z*-combretatstatin A-4 TBDMS ether **8** was accomplished by treatment with KF-$2H_2O$ in methanol at room temperature for 2 h to provide pure *Z*-combretastatin A-4 **1** in 95% yield after chromatographic workup.

In summary, the iron(III)-catalyzed Kumada–Corriu cross-coupling reaction has been utilized in a efficient way to reach the biologically active stilbene combretastatin A-4 from inexpensive starting materials in a 40% overall yield. This route can also be applied to the synthesis of other more potent analogs of **1**.

EXPERIMENTAL

THF was distilled from sodium-benzophenone under argon atmosphere. Thin-layer chromatography (TLC) was performed on SiO_2 plates. SiO_2 (70–230 mesh) was used for column chromatography. NMR was obtained with a Varian Gemini XL200 or Varian Unity at 400 MHz with $CHCl_3$ signal as internal reference. All coupling reactions were done under argon using flame-dried glassware.

cis + *trans*-3,4,5-Trimethoxybromostyrene (6)

To a stirred solution of 3,4,5-trimethoxycinnamic acid (8.8 g, 37 mmol) in chloroform (55 mL), a solution of bromine (6.24 g, 39 mmol) in chloroform (10 mL) was added dropwise at room temperature. After the addition, the reaction mixture was stirred 1 h more and then the chloroform was removed in vacuo to afford the dibromo acid as a solid residue. The crude dibromoacid was dissolved in DMF (50 mL) and cooled at 0 °C in an ice-water bath. Then Et_3N (11.53 g, 114 mmol) was added dropwise. The reaction mixture was stirred while reaching room temperature, and the stirring continued for 8 h. The reaction mixture was partitioned

between water and chloroform (100 mL). The layers were separated, and the aqueous phase extracted with chloroform. The combined organic extracts were washed successively with water (4×100 mL), 3 N HCl (100 mL), and saturated $NaHCO_3$ solution and dried over Na_2SO_4. Solvent removal in vacuo afforded a brown oil, which was purified by column chromatography (SiO_2) eluting with hexane/EtOAc (9/1) to afford 8.99 g (89%) of a 82:18 mixture of *cis*- and *trans*-3,4,5-trimethoxybromostyrene as an oil. ^{1}H NMR δ: 3.83–3.90 (*E* and *Z*-OCH_3 9.1 H), 6.37 (0.80 H, d, $J = 8.4$ Hz, *Z*), 6.51 (0.35 H, s, *E*), 6.68 (0.27H, d, $J = 13.92$ Hz, *E*), 6.95–7.05 (2.63 H, m).

5-Bromo-2-methoxyphenol (10)

NBS (9.43 g, 53 mmol) was added to a solution of guaiacol acetate (8 g, 48 mmol) in acetonitrile (120 mL), and the reaction mixture was heated at 60°C during 12 h. The reaction mixture was diluted with EtOAc (150 mL) and quenched with water (150 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with aqueous sodium sulfite solution, water, and brine. Solvent removal afforded a viscous oil, which was dissolved in methanol, and then a solution of KOH (5.6 g, 100 mmol) in methanol was added. The mixture was refluxed under argon for 5 h and then acidified with 6 N HCl (50 mL). The reaction was extracted with CH_2Cl_2 (100 mL), and the aqueous layer was extracted again with CH_2Cl_2. The combined organic extracts were washed with water and brine and dried (Na_2SO_4). Solvent removal and chromatography of the residue (SiO_2) eluting with hexane/EtOAc (8/2) afforded bromophenol **10** as crystals (8.0 g, 82%), mp 101–103°C. ^{1}H NMR δ: $CDCl_3$: 3.76 (s 3H), 6.58 (d, 1H), 6.83–6.89 (d, 1H), 6.97 (d, 1H).

5-Bromo-2-methoxyphenol t-Butyldimethylsilyl Ether (11)

t-Butyldimethylchlorosilane (5 g, 33.17 mmol) was added to a stirred solution of 5-bromo-2-methoxyphenol (6.66 g, 32.8 mmol) and imidazole (4.53 g, 66 mmol) in DMF (20 mL). The reaction mixture was stirred 16 h at room temperature, and then the mixture was partitioned between hexanes and water. After separation of the phases, the organic layer was washed with water and dried (Na_2SO_4). Solvent removal in vacuo afforded TBS ether **11** as an oil (9.95 g, 96%). This was pure enough to be used without further purification.

^{1}H NMR δ: $CDCl_3$: 0.15 (s, 6H), 0.99 (s, 9H), 3.78 (s, 3H), 6.69 (1H, d, $J = 8.4$ Hz), 6.99 (d, 1H, $J = 1.7$ Hz), 7.20 (1H, dd, $J = 8.4$ and 1.7 Hz).

tert-Butyldimethylsilyl Ether of Combretastatin A-4 (8)

To an ice-cooled (−5 to 0 °C) solution of the mixture of bromostyrenes **6** (2.73 g, 10 mmol) and 265 mg (5 mol%) of [Fe(acac)$_3$] in a mixture of THF (20 mL), and NMP (2 mL), a solution of the Grignard **7** reagent prepared from 4.75 g (15 mmol, 1.5 equiv) of 5-bromo-2-methoxyphenol *t*-butyldimethylsilyl ether **11** and magnesium (600 mg) in THF (25 mL) was added dropwise via syringe. After the addition, stirring continued for 30 min, and then the reaction mixture was quenched by addition of saturated NH_4Cl solution (50 mL). The phases were separated, and the aqueous layer was extracted with Et_2O. The combined organic phases were washed with brine and dried (Na_2SO_4). Solvents were removed in vacuo, and the residue was purified by column chromatography (SiO_2) to afford 2.63 g (61% yield) of CA-4 TBS ether **8** as an oil. ^{1}H NMR δ: $CDCl_3$: 6.71–6.88 (m, 3H), 6.50 (s, 2H), 6.45 (d, 2H, $J = 12$), 3.83 (s 3H), 3.78 (s, 3H), 3.70 (s, 6H), 0.93 (s, 9H), 0.05 (s, 6H).

^{13}C NMR δ: $CDCl_3$: 153.1, 150.5, 144.8, 133.3, 130.25, 129.9, 128.9, 123.1, 121.5, 111.85, 106.07, 61.1, 56.1, 55.7, 25.9, 18.6, −4.55. IR (NaCl neat): 3000, 2955, 2933, 2858, 2838, 1580, 1511, 1505, 1464, 1455, 1424, 1391, 1361, 1327, 1281, 1236, 1184, 1156, 1129, 1032, 1110, 995, 963, 813, 784 cm^{-1}. The spectral data for this compound were identical to those reported.[10]

Combretastatin A-4 (1)

Potassium fluoride dihydrate (1 g) was added to a solution of the silyl ether **8** (1 g, 2.32 mmol) in methanol (10 L). The mixture was stirred under argon. TLC monitoring of the reaction showed the disappearance of starting material after 40 min. After this time, the mixture was diluted with dichloromethane (10 mL) and quenched with water (10 mL). The phases were separated, and the aqueous layer was extracted with dichloromethane in three portions. The combined organic extracts were washed with water and dried (Na_2SO_4). Solvent removal and chromatography of the residue on SiO_2 (hexane/EtOAc 4:1 → 2:1) afforded a viscous oil that slowly solidified on standing (0.797 g, 92% yield). ^{1}H NMR δ: $CDCl_3$: 6.92 (d, 1H, $J = 1.82$), 6.80 (1H, dd, $J = 2$, 8.4), 6.73 (d, 1H, $J = 8.4$), 6.52 (s, 2H), 6.44 (d, 2H, $J = 12$), 5.51 (s, 1H, br), 3.87 (s, 3H), 3.84 (s, 3H), 3.70 (s, 6H).13C NMR δ: $CDCl_3$: 153.07, 146.02, 145.45, 137.34,

132.93, 130.81, 129.71, 129.22, 121.32, 115.27, 110.56, 106.28, 61.15, 56.15. IR (neat) NaCl: 3426, 3004, 2938, 2837, 1614, 1579, 1508, 1462, 1456, 1419, 1328, 1274, 1237, 1182, 1127, 1027, 1005, 881, 855, 794, 761 cm^{-1}. The spectral data of this compound were identical to those reported.[10]

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