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A new synthesis of combretastatins A-4 and AVE-8062A

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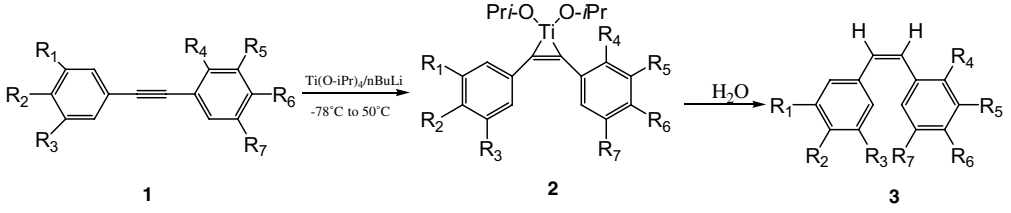
Abstract—Combretastatins A-4 and AVE-8062A have been synthesized by coupling 3,4,5-trimethoxyphenylacetylene with the corresponding iodomethoxyphenol and bromomethoxyaniline, followed by hydrolysis of the thermally-stable Ti(II)–alkyne complexes.

Combretastatins are an important group of anticancer drugs,[1] isolated from the African tree *Combretum caffrum*. In particular, *cis*-combretastatins A-4 and AVE-8062A disrupt tubulin aggregation, thereby preventing metastasis and angiogenesis, which places them among the most active of antineoplastic agents.[2] An efficient synthesis of these compounds would offer an opportunity to perform wider studies, given their low availability due to the poor bark content. Specifically, as part of our project aimed at improving the low water solubility of these compounds, we required sufficient quantities of both combretastatins. Therefore, a new synthetic method that offers access to both *cis*-A-4 and *cis*-AVE-8062A is described herein. We also include other examples of *cis*-stilbenes, which were prepared in order to test the wider applicability of our method.

Cis-isomers **3** are usually synthesized by alkyne hydroboration,[3] selective alkyne reduction using Lindlar's catalyst,[4] or by Wittig condensation;[5] all of these methods are associated with different complications. Mixtures of *Z*- and *E*-isomers are inevitably formed from Wittig reactions, which require complex chromatographic separations.[1c]

Partial hydrogenation provides combretastatin A-4 together with a minor amount of the corresponding alkane, which can only be removed by preparative HPLC[4] or else requires additional protection to facilitate separation. On looking for another way to selectively obtain alkenes **3**, we found a report[6] on a cross-coupling reaction of thermally stable titanium(II)–alkyne complexes with aryl halides, and we tested this method as a means of obtaining the corresponding combretastatins. The procedure involves



1 **2** **3** (1)

hydrolysis of the corresponding Ti(II)–diarylalkyne complexes **2**, prepared from diarylalkynes **1**, Ti(O–*i*Pr)$_4$, and *n*BuLi at −78 °C. The thermally stable Ti(II)–alkyne complexes **2** were successfully generated by slow addition of 4 equiv of *n*BuLi as a reducing agent to a mixture of Ti(O–*i*Pr)$_4$ (2 equiv) and alkyne **1**

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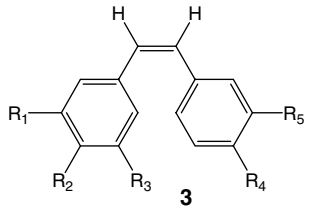
Table 1. Selective reduction of diarylalkynes



3

3a COMBRETASTATIN A-4
3b COMBRETASTATIN AVE-8062A

Entry	R_1	R_2	R_3	R_4	R_5	Mp[c] (°C)	Yield[a] (%)
3a	OMe	OMe	OMe	OMe	OH	83.81[d]	94[b]
3b	OMe	OMe	OMe	OMe	NH_2	Oil	86[b]
3c	OMe	OMe	OMe	H	H	Oil	90
3d	OMe	OMe	OMe	H	NH_2	79.11	92
3e	NH_2	H	H	OMe	OMOM	Oil	79
3f	H	H	H	OMe	OH	43.62	83

[a] Yields refer to isolated yields.
[b] Both combretastatins gave satisfactory ^{1}H NMR and IR spectral data.[3a,5,9]
[c] Melting points were determined on a Mettler-Toledo 822e differential scanning calorimeter.
[d] Lit.: 84.5–85.5 °C.[1b]

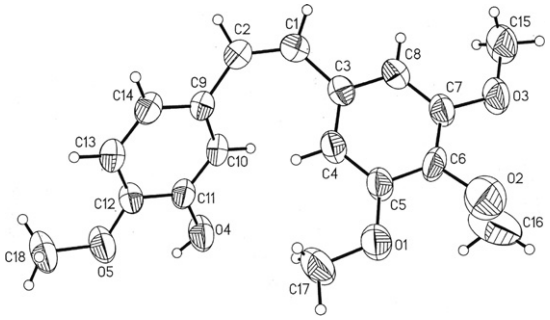


Figure 1. X-ray crystal structure of combretastatin A-4.[7]

(1 equiv) in THF at −78 °C, and then increasing the temperature to 50 °C (Eq. 1). The solution of **2** in THF thus obtained was stirred for an additional 1 h at 50 °C and was then hydrolyzed to selectively afford *cis*-stilbenes **3** in good yields and high purity (Table 1). Indeed, this high purity enabled us to perform the first single-crystal X-ray structure determination of combretastatin A-4 (Fig. 1).[7] Previously, the combretastatin pioneering group of Pettit has reported a crystal structure of *cis*-A-4 phosphate.[8]

As regards the synthesis of diarylalkynes **1**, we employed an approach similar to that described recently.[3a,c] However, our protocol does not involve the use of a Cu catalyst, which necessitates special experimental conditions, and we found a way of avoiding the use of a protecting group.

In a first attempt (Method 1), we used a Sonogashira coupling[10] of arylalkynes **4**[11] and aryl halides **5**[12] in the presence of $Pd(OAc)_2$, DABCO, and Cs_2CO_3, with acetonitrile as solvent, for the synthesis of the requisite diarylalkynes. These reaction conditions proved to be very efficient for iodinated precursors (Table 2, entries B, D, and E). Nonetheless, the strongly basic conditions necessitated hydroxyl protection. Reaction in the case of the substituents indicated in Entry A did not give the desired product, but when the hydroxyl was protected as an MOM ether, the precursor of combretastatin A-4 was obtained in 80% yield. 5-Bromo-1,2,3-trimethoxybenzene was not reactive under these conditions (entry C). Therefore, the combretastatin AVE-8062A precursor, which also needs to be prepared from a brominated compound, could not be obtained in this way. Results pertaining to Method 1 are listed in Table 2.

In a second attempt (Method 2), we employed a method described for the coupling of vinyl and aryl halides with terminal alkynes,[13] using $Pd(OAc)_2$ and triphenylphosphine in refluxing pyrrolidine. These reaction conditions worked very well for both the iodinated and brominated precursors, and hydroxyl protection was not necessary. When the starting materials corresponding to entries A and C in Table 2 were subjected to the conditions of Method 2, the isolated yields were 95% and 93%, respectively,[14] clearly indicating the advantage of this method. The precursor of combretastatin AVE-8062A (entry H) was obtained in low yield (58%), probably due to the unstable nature of the bromomethoxyaniline under these reaction conditions.

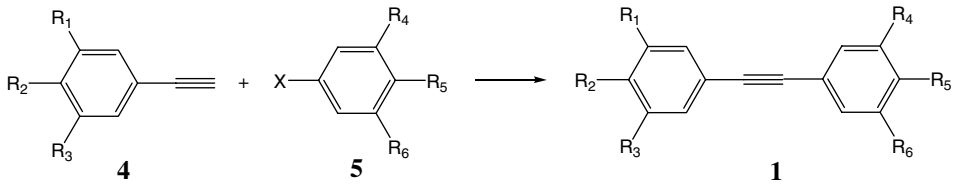
Several iodinated and brominated compounds were coupled with different terminal arylalkynes, and the results are shown in Table 2.

In summary, two combretastatins, A-4 and AVE-8062A, have been synthesized by means of a new and simple method, in yields comparable to those of previous literature syntheses, enabling a more effective production of these antineoplastics, in respect to more predictable yields of the cis-isomers.

Typical procedure for the preparation of 2-(3″-hydroxy-4″-methoxyphenyl)-1-(3′,4′,5′-trimethoxyphenyl)ethyne (Method 2, entry A)

To a stirred solution of 3,4,5-trimethoxyphenylethyne[3a] (576 mg, 3.0 mmol) and 5-iodo-2-methoxyphenol[3a]

Table 2. Palladium-catalyzed coupling of arylalkynes and arylhalides



Entry	R_1	R_2	R_3	X	R_4	R_5	R_6	Mp[f] (°C)	Yield[g] (%)
A[a,c]	OMe	OMe	OMe	I	OH	OMe	H	—	0
B[a]	OMe	OMe	OMe	I	OMOM	OMe	H	105.38	80
C[a]	H	H	H	Br	OMe	OMe	OMe	—	0
D[a]	H	H	H	I	OMOM	OMe	H	57.9	85
E[a]	NH_2	H	H	I	OMOM	OMe	H	110.2	49
A[b,c]	OMe	OMe	OMe	I	OH	OMe	H	97.4[e]	95
B[b]	OMe	OMe	OMe	I	OMOM	OMe	H	105.3	71
C[b]	H	H	H	Br	OMe	OMe	OMe	73.6	93
D[b]	H	H	H	I	OMOM	OMe	H	59.17	98
E[b]	NH_2	H	H	I	OMOM	OMe	H	109.7	84
F[b]	NH_2	H	H	Br	OMe	OMe	OMe	125.03	88
G[b]	H	H	H	I	OH	OMe	H	109.5	88
H[b,d]	OMe	OMe	OMe	Br	NH_2	OMe	H	96.29	58

[a] Method 1: $Pd(OAc)_2$, DABCO, Cs_2CO_3, CH_3CN, room temperature to reflux, 24–72 h.[10]
[b] Method 2: $Pd(OAc)_2$, PPh_3, pyrrolidine, reflux.[13]
[c] Combretastatin A-4 precursor.
[d] Combretastatin AVE-8062A precursor.
[e] Lit.: 96–98 °C.[4]
[f] Melting points were determined on a Mettler-Toledo 822e differential scanning calorimeter.
[g] Yields refer to isolated yields.

(500 mg, 2.0 mmol) in pyrrolidine (5.0 mL) under an argon atmosphere were added PPh_3 (21 mg, 0.08 mmol) and $Pd(OAc)_2$ (9.0 mg, 0.04 mmol). After stirring at reflux for 30 min, the mixture was hydrolyzed with a saturated aqueous solution of ammonium chloride (30 mL) and extracted with dichloromethane (30 mL). The organic extract was dried over Na_2SO_4 and the solvent was removed in vacuo. Chromatography (silica gel; hexane/EtOAc, 8:2) gave diarylalkyne **1**[A[b]] (600 mg, 95%) as a thick oil that subsequently solidified. Recrystallization (hexane/dichloromethane) gave colorless crystals, mp 97.4 °C.

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7. X-ray structure analysis of combretastatin A-4: Bruker Smart CCD diffractometer, Mo-Kα-radiation ($\lambda = 0.71073$ Å), $T = 298$ (2) K. Crystal size: $0.33 \times 0.16 \times 0.08$ mm^3, colorless, prism, space group $P21/n$, monoclinic, $a = 6.816$ (8)°, $b = 24.265$ (3)°, $c = 10.4219$ (13)°, $\beta = 107.604$ (2)°, $V = 1642.5$ (10) Å^3, $Z = 4$, $\rho_{cal} = 1.279$ g/cm^3, $\theta_{range} = 2.22$–24.39°, 13021 reflections collected, 2889 independent ($R_{int} = 0.0498$), 215 parameters and 99.9% completeness to theta = 25.0°. Final R indices [$I/2\sigma$], $R = 0.65$, $Rw = 0.11$. Structure solution: direct methods (SHELXTL V 6.14), refinement on F_2 (SHELEXTL V 6.14). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 646589.
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9. Spectral data of combretastatins and *cis*-arylalkenes: Compound **3a**: IR (KBr) $v = 3453$ (br), 3006 (m), 1616 (w), 1580 (s), 1327 (m), 1238 (s), 1126 (s), 1010 (w) cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): $\delta = 3.698$ (6H, s, OMe), 3.842 (3H, s, OMe), 3.866 (3H, s, OMe), 5.520 (1H, s, OH), 6.408 (1H, d, $J = 12$ Hz, CH═C), 6.473 (1H, d, $J = 12$ Hz, C═CH), 6.527 (2H, s, H-2′, 6′), 6.731 (1H, d, $J = 8.1$ Hz, H-5″), 6.798 (1H, dd, $J = 8.5$, 1.9 Hz, H-6″), 6.923 (1H, d, $J = 2.0$ Hz, H-2″).

Compound **3b**: IR (film) $v = 3473$ (w), 3370 (w), 3001 (m), 2936 (m),1613 (m), 1578 (s), 1326 (m), 1233 (s), 1005 (w) cm^{-1}. ^{1}H NMR (200 MHz; $CDCl_3$): $\delta = 3.708$ (6H, s, OMe), 3.834 (3H, s, OMe), 3.842 (3H, s, OMe), 6.372 (1H, d, $J = 12.2$ Hz, CH═C), 6.466 (1H, d, $J = 12$ Hz, C═CH), 6.551 (2H, s, H-2′, 6′), 6.696 (2H, m, H-5″, 6″), 6.747 (1H, s, H-2″).

Compound **3c**: IR (film) $v = 2997$ (w), 2936 (w), 1579 (s), 1327 (m), 1236 (s), 1125 (s), 1006 (w) cm^{-1}. ^{1}H NMR (200 MHz; $CDCl_3$): $\delta = 3.648$ (6H, s, OMe), 3.832 (3H, s, OMe), 6.464 (2H, s, H-2′-6′), 6.495 (1H, d, $J = 12.4$ Hz, CH═C), 6.610 (1H, d, $J = 12.4$ Hz, C═CH), 7.244 (5H, m, H-Ph″). MS (m/z) EI = 270 (M^+).

Compound **3d**: IR (KBr) $v = 3447$ (s), 3365 (s), 3008 (m), 1633 (m), 1597 (m), 1582 (m), 1326 (m), 999 (m) cm^{-1}. ^{1}H NMR (200 MHz; $CDCl_3$): $\delta = 3.680$ (6H, s, OMe), 3.833 (3H, s, OMe), 6.436 (1H, d, $J = 12.0$ Hz, CH═C), 6.533 (1H, d, $J = 12.0$ Hz, C═CH), 6.520 (2H, s, H-2′, 6′), 6.540 (d, 1H, $J = 7.6$, H-6″), 6.634 (1H, m, H-2″), 6.706 (1H, d, $J = 7.6$ Hz, H-4″), 7.063 (1H, t, $J = 7.7$ Hz, H-5″). MS (m/z) EI = 285 (M^+).

Compound **3e**: IR (film) $v = 3457$ (w), 3367 (w), 3002 (w), 2953 (w), 1619 (m), 1597 (m), 1580 (m), 1508 (s), 1261 (s), 993 (s) cm^{-1}. ^{1}H NMR (200 MHz; $CDCl_3$):$\delta = 3.430$ (3H, s, OCH_3), 3.574 (2H, br, NH_2), 3.857 (3H, s, OCH_3), 5.069 (2H, s, CH2), 6.451 (2H, s, CH═CH), 6.531 (1H, ddd, $J = 7.8$, 2.4, 1.0 Hz, H-6′), 6.656 (1H, m, H-2′), 6.699 (1H, t, $J = 1.2$ Hz, H-4′), 6.761 (1H, d, $J = 8.2$ Hz, H-5″), 6.920 (1H, dd, $J = 8.4$, 2.0 Hz, H-6″), 7.046 (1H, t, $J = 8.2$ Hz, H-5′), 7.107 (1H, d, $J = 7.2$ Hz, H-2″). MS (m/z) EI = 285 (M^+).

Compound **3f**: IR (KBr) $v = 3417$ (br), 3023 (m), 2841 (m), 1589 (m), 1513 (m),1343 (m), 1119 (s), 1023 (s) cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): $\delta = 3.854$ (3H, s, OCH_3), 5.480 (1H, s, OH), 6.472 (1H, d, $J = 12.0$ Hz, CH═C), 6.519 (1H, d, $J = 12.3$ Hz, C═CH), 6.691 (1H, d, $J = 8.4$ Hz, H-5″), 6.748 (1H, dd, $J = 8.4$, 1.8 Hz, H-6″), 6.835 (1H, d, $J = 2.1$ Hz, H-2″), 7.229 (5H, m, H-Ph′). MS (m/z) EI = 226 (M^+).

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14. Spectral data of diarylalkynes: entry A: IR (KBr) $v = 3479$ (br), 2935 (m), 2218 (w), 1575 (s), 1506 (s), 1233 (s), 1125 (s) cm^{-1}. ^{1}H NMR (200 MHz; $CDCl_3$): $\delta = 3.869$ (3H, s, OCH_3), 3.882 (6H, s, OCH_3), 3.922 (3H, s, OCH_3), 5.614 (1H, s, OH), 6.757 (2H, s, H-2′, 6′), 6.823(1H, d, $J = 8.0$ Hz, H-5″), 7.071 (1H, dd, $J = 8.0$ Hz, 2.0 Hz, H-6″), 7.09 (1H, d, $J = 2.0$ Hz, H-2′). Entry B: IR (KBr) $v = 2956$ (br), 2836 (m), 2211 (w), 1574 (s), 1511 (s), 1244 (s), 1129 (s) cm^{-1}.