Novel Syntheses of Cis and Trans Isomers of Combretastatin A-4

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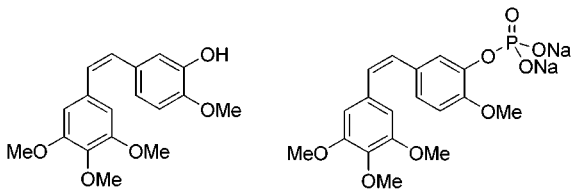
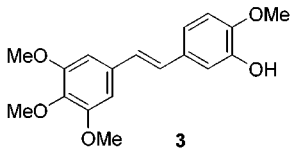
A high-yielding, two-step stereoselective synthesis of the anticancer drug (*Z*)-combretastatin A-4 (**1**) has been devised. The method uses the Perkin condensation of 3,4,5-trimethoxyphenylacetic acid and 3-hydroxy-4-methoxybenzaldehyde followed by decarboxylation of the cinnamic acid intermediate using copper and quinoline. The iodine-catalyzed isomerization of the *Z* isomer **1** results in complete conversion to the *E* isomer. The Suzuki cross-coupling of an aryl boronic acid and vinyl bromide has also been successfully employed to produce both *Z* and *E* isomers of combretastatin A-4 stereoselectively. Both methods are far superior to the current five-step Wittig synthesis in which both isomers are produced nonstereoselectively.

Introduction

The combretastatins are a group of antimitotic agents isolated from the bark of the South African tree *Combretum caffrum*. The most potent of these is combretastatin A-4[1] which has been found to be a potent cytotoxic agent which strongly inhibits the polymerization of tubulin by binding to the colchicine site.[2] Combretastatin A-4 (**1**) is also able to elicit irreversible vascular shutdown within solid tumors, leaving normal vasculature intact.[3] A prodrug of combretastatin A-4, the water soluble phosphate derivative[4] **2** is now in phase II of clinical trials.





Structure activity relationship analyses of the combretastatins indicate that the cis configuration of the stilbene unit is the most important factor for inhibition of cancer cell growth.[5] *E* stilbenes show a dramatic decrease in their inhibitory effects on cancer cell growth and tubulin polymerization when compared to their corresponding *Z* isomers.

Most syntheses of the combretastatins and analogues utilize the Wittig reaction.[2c,5] The route developed by Pettit et al.[5c] is representative. They reported a five-step method from 3,4,5-trimethoxybenzyltriphenylphosphonium bromide and isovanillin using *n*-butyllithium as the base. Both cis **1** and trans **3** isomers of combretastatin A-4 were produced in a ratio of 1:1.5, with the overall yield of the cis isomer being 19%. The best selectivity reported was obtained on reaction of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide with the bis-*tert*-butylphosphate ester of isovanillin.[5f] A 4:1 mixture of *Z*:*E* stereoisomers was obtained in a route to the prodrug **2**. The Wittig method is, therefore, problematic on two counts. First, owing to the lack of or poor stereoselectivity, the yield of the desired *Z* isomer is reduced, and, second, a separation process is required. The isomers of combretastatin A-4 are difficult to separate, particularly by chromatography.

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Furstner et al.[6] have developed a stereoselective method based on the Lindlar-type semihydrogenation of an alkyne precursor (assembled by 9-MeO-9-BBN-mediated Suzuki-type cross-coupling). This was *Z* selective with a small amount of the corresponding alkane also isolated ((*Z*)-combretastatin A-4:alkane 86:14). This methodology has been developed further, eliminating the use of protecting groups and constructing the alkene moiety with greater stereoselectivity.[7] However, both these methods[6,7] have shortcomings and are not ideal for large-scale applications.

The purpose of this study was, therefore, to investigate novel methods of stereoselective syntheses of cis **1** and trans **3** isomers of combretastatin A-4. The development of a route amenable to the large-scale production of combretastatin A-4 was our main goal. It was also desirable to develop a stereoselective synthesis of the *E* isomer, which could be applied to the preparation of other related stilbenes. This is most important for their accurate biological assessment, as it is critical that the trans isomer is not contaminated by trace quantities of their more active cis counterparts. In some cases, we have found that the cis isomer is 10 000 times more active than the trans isomer.

Results and Discussion

There are a number of examples in the literature of substituted stilbenes being produced using the Suzuki cross-coupling of an ethenyl halide and aryl boronic acid,[8] and we considered that the synthesis of combretastatin A-4 and its trans equivalent might similarly be achieved.

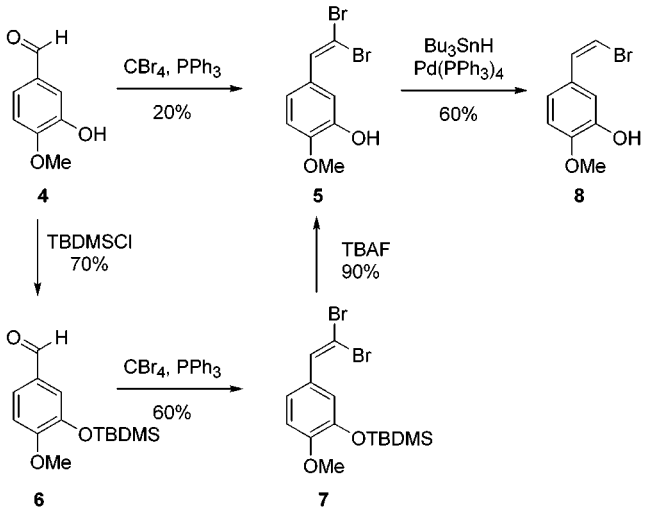
(*Z*)-5-(2′,2′-Dibromoethenyl)-2-methoxyphenol (**5**) was synthesized using the Corey−Fuchs Wittig-like bromination of 3-hydroxy-4-methoxybenzaldehyde (**4**).[9] The yield was poor (ca. 20%), and, consequently, the reaction was repeated with silyl protection of the phenol.[1c,19] Deprotection of the dibromostyrene (**7**), derived from the aldehyde **6**, using tetrabutylammonium fluoride gave an improved overall yield of the required phenol **5** (ca. 40%). Stereoselective reduction of the phenol **5** using tributyltin hydride and tetrakis(triphenylphosphine)palladium(0)[10] afforded (*Z*)-5-(2′-bromoethenyl)-2-methoxyphenol (**8**) in good yield (ca. 60%) following purification by column chromatography and recrystallization (Scheme 1).

The *(Z)*-vinyl bromide **8** was reacted with the boronic acid **9** in 1,2-dimethoxyethane (DME), according to the method of Strachan et al.[11] Tetrakis(triphenylphosphine)-palladium(0) was employed as the catalyst for the reaction, and aqueous Na_2CO_3 provided the basic environment required. Flash column chromatography, followed by recrystallization, afforded (*Z*)-combretastatin A-4 (**1**) in good yield (ca. 70%) (Scheme 2). GC analysis of the compound following purification indicated that the *Z*:*E* ratio was 99:1. The combretastatin A-4 sample was found to contain <0.5% tin and <0.4% palladium. The overall yield of combretastatin A-4 from isovanillin (**4**) was 16%.

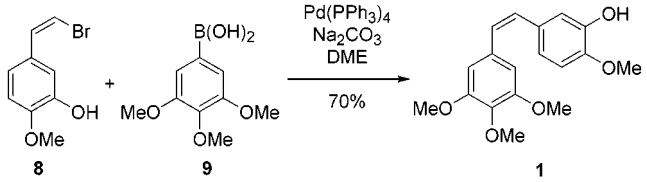
The synthesis of (*E*)-combretastatin A-4 (**3**) by the same method required the (*E*)-vinyl bromide **11**. Bromination of inexpensive 3-hydroxy-4-methoxycinnamic acid (**10**) in acetic acid produced this vinyl bromide **11** in moderate yield (ca. 30%) (Scheme 3).[12] The cis and trans configurations of the vinyl bromides **8** and **11** were confirmed by measuring the characteristic coupling constants of the olefinic protons in the NMR spectra. These were 8 Hz for **8** and 14 Hz for **11**.

(*E*)-5-(2-Bromoethenyl)-2-methoxy-phenol (**11**) was reacted with 3,4,5-trimethoxybenzene boronic acid (**9**) as described above. The reaction produced trans combret-

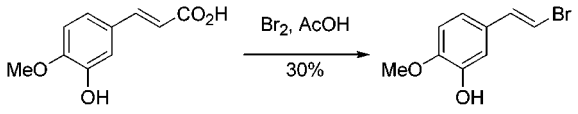
Scheme 1. Synthesis of (*Z*)-5-(2′-Bromoethenyl)-2-methoxyphenol from 3-Hydroxy-4-methoxybenzaldehyde



Scheme 2. Synthesis of the *Z* Isomer of Combretastatin A-4 Using the Palladium-Catalyzed Suzuki Cross-Coupling of (*Z*)-5-(2′-Bromoethenyl)-2-methoxyphenol and 3,4,5-Trimethoxybenzene Boronic Acid



Scheme 3. Synthesis of (*E*)-5-(2′-Bromoethenyl)-2-methoxyphenol from 3-Hydroxy-4-methoxycinnamic Acid



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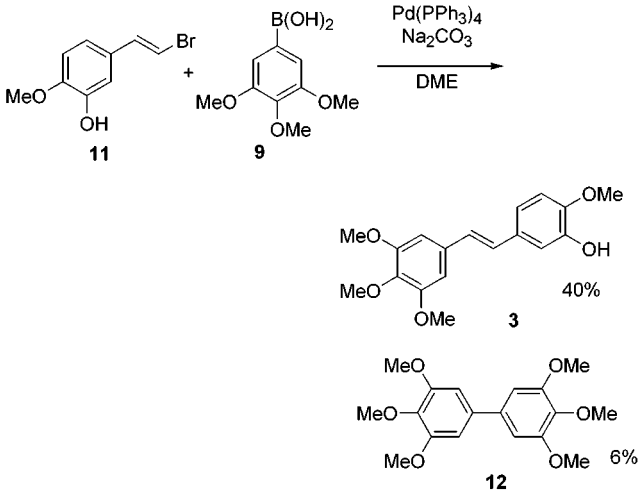
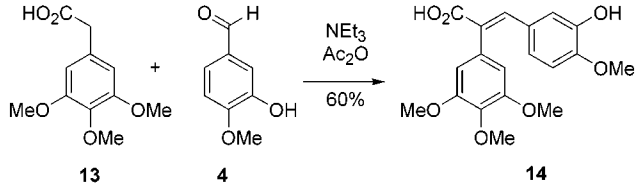
Scheme 4. Synthesis of the *E* Isomer of Combretastatin A-4 Using the Palladium-Catalyzed Suzuki Cross-Coupling of (*E*)-5-(2′-Bromoethenyl)-2-methoxyphenol and 3,4,5-Trimethoxybenzene Boronic Acid



Scheme 5. Perkin Condensation of 3,4,5-Trimethoxyphenylacetic Acid and 3-Hydroxy-4-methoxybenzaldehyde



astatin A-4 (**3**) in moderate yield (ca. 40%) and 3,3′,4,4′,-5,5′-hexamethoxybiphenyl[20] (**12**) in low yield (ca. 6%) (Scheme 4).

While the Suzuki cross-coupling syntheses of cis and trans combretastatin A-4 were successful, we were keen to develop more efficient processes. We next investigated the synthesis of the stilbenes using the Perkin condensation,[13] described by Letcher et al.[14] The reaction involved heating 3,4,5-trimethoxyphenylacetic acid (**13**) (2 equiv), 3-hydroxy-4-methoxybenzaldehyde (**4**) (1 equiv), triethylamine, and acetic anhydride at reflux. Upon cooling, the reaction mix was acidified with concentrated hydrochloric acid, and the cinnamic acid, **14**, precipitated from the solution. This acid **14** was isolated and recrystallized from ethanol in good yield (ca. 60%) (Scheme 5).

We were unable to grow a suitable crystal of cinnamic acid **14** for X-ray crystallography or obtain useful data on the stereochemistry from an NOE spectrum. The extinction coefficient, measured from the UV spectra, is known to be much greater for stilbenes in which the aromatic rings are trans to each other (ϵ ca. 28 000), rather than for those in which the aromatic rings are cis to each other (ϵ ca. 10 000).[15] We found the extinction coefficient for cinnamic acid **14** to be 11 100, which supports our belief that the configuration of the molecule is *E*. Cinnamic acid **14** was first converted to the methyl ester[5b] **15** and then reduced to the alcohol[16] **16** (Scheme 6). The stereochemistry of this compound was determined by assessing diagnostic cross-peak signals in the NOESY ^{1}H spectra of alcohol **16**. In the spectra, the CH_2 protons of alcohol **16** form cross-peaks with both the olefinic proton and aromatic protons, 2′ and 6′ on the A ring, indicating that the aromatic rings are cis to each other and that the overall configuration is *E*.

Decarboxylation of the acid **14** was achieved using powdered copper and quinoline at 230 °C, following the method of Molho et al.[17] (Scheme 7). Initially cis combretastatin A-4 (**1**) was purified in good yield (ca. 70%) using flash column chromatography (*Z*:*E* 99.4:0.6). A small amount of the trans isomer **3** was also isolated (ca. 10%), but on repetition of the reaction, it was found that the cis isomer could be purified by recrystallization alone (ca. 72%). GC analysis of the crude reaction mix showed a *Z*:*E* ratio of 88:12, but following recrystallization this changed to 99.8:0.2. The sample was analyzed for copper content, but only a trace amount could be detected (0.006%). Clearly this represents an efficient stereoselective synthesis of cis combretastatin A-4 (**1**), which avoids the use of protecting groups and chromatography.

This efficient synthesis of (*Z*)-combretastatin A-4 (**1**) renders it suitable for the synthesis of the trans isomer. There is a literature precedent for the iodine-catalyzed isomerization of cis stilbenes.[18] When iodine (10 mol %) is added to a solution of cis combretastatin A-4 (**1**) in chloroform and the resulting mixture is stirred at room temperature for 30 min, complete isomerization to trans combretastatin A-4 (**3**) occurs (Scheme 8). Following workup, trans combretastatin A-4 is afforded in quantitative yield [*E*:*Z*, 99.8:0.2 (determined by GC)].

Conclusions

We have devised two methods of synthesis of cis combretastatin A-4 (**1**) in which the stereoselectivity is much improved on the current Wittig method of synthesis. The route based on the Perkin condensation, which avoids the use of protecting groups and chromatography, is ideally suited for large-scale applications.

Experimental Section

General Methods. All reagents and chromatography grade solvents were obtained from commercial sources and used without further purification unless indicated. Flash column chromatography was performed on silica gel [Fluka Silica gel 60 220−440 mesh (35−70 μm)], and TLC was carried out using silica (0.2 mm, 60 F_{254})-precoated, aluminum-backed plates. Elemental analyses were carried out by the Microanalytical department at UMIST and are within 0.4% of theoretical values.

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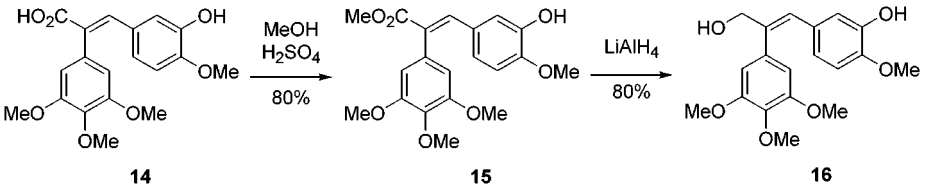
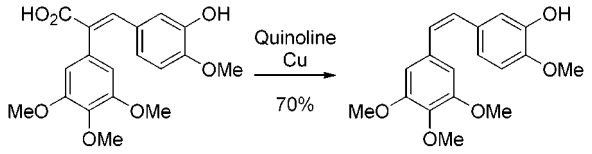
Scheme 6. Esterification and Reduction of Cinnamic Acid 14



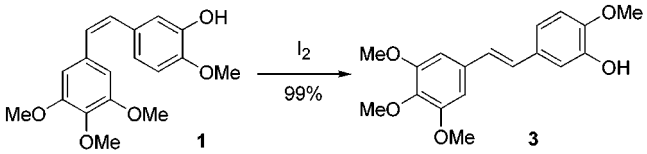
14 **15** **16**

Scheme 7. Synthesis of Combretastatin A-4 by Decarboxylation of Cinnamic Acid 14



14 **1**

Scheme 8. Synthesis of the *E* Isomer of Combretastatin A-4 by Isomerization of the *Z* Isomer Using Iodine



1 **3**

Cis Combretastatin A-4 (1). (*Z*)-5-(2-Bromoethenyl)-2-methoxyphenol (**8**) (300 mg, 1.31 mmol) and tetrakis(triphenylphosphine)palladium(0) (75 mg, 0.065 mmol) were stirred in 1,2-dimethoxyethane (20 mL) under argon for 20 min. 3,4,5-Trimethoxybenzene boronic acid (315 mg, 1.49 mmol) and sodium carbonate (140 mg, 1.32 mmol) in water (12 mL) were added, and the mixture was heated at reflux overnight. The aqueous layer was separated and extracted with chloroform. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Following flash column chromatography (SiO_2 petrol:EtOAc 7:3), cis combretastatin A-4 (**1**) was isolated as a pale yellow crystalline solid (295 mg, 71%). mp 117−118 °C (lit. mp[5c] 116 °C). R_f = 0.46 (SiO_2 petrol:EtOAc 1:1). δ_H (300 MHz, $CDCl_3$): 3.72 (6H, s), 3.86 (3H, s), 3.89 (3H s), 5.53 (1H, s), 6.42 (1H, d, J = 12.4), 6.49 (1H, d, J = 12.4), 6.55 (2H, s), 6.75 (1H, d, J = 8.3), 6.82 (1H, dd, J = 8.3, 1.9), 6.94 (1H, d, J = 1.9). Elemental analysis of palladium content: none detected (<0.4%). Elemental analysis of tin content: none detected (<0.5%).

Trans Combretastatin A-4 (3). (*E*)-5-(2-Bromoethenyl)-2-methoxyphenol (**11**) (285 mg, 1.24 mmol) and tetrakis-(triphenylphosphine)palladium(0) (72 mg, 0.062 mmol) were stirred in 1,2-dimethoxyethane (20 mL) under argon for 20 min. 3,4,5-Trimethoxybenzene boronic acid (**9**) (300 mg, 1.42 mmol) and sodium carbonate (131 mg, 1.24 mmol) in water (11 mL) were added, and the mixture was heated at reflux overnight. The aqueous layer was separated and extracted with chloroform. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography (SiO_2 petrol:EtOAc 7:3) afforded stilbene **3** (158 mg, 40%) as an off-white solid. mp 102−104 °C (lit. mp[5c] 103−104 °C). R_f = 0.41 (SiO_2 petrol: EtOAc 1:1). δ_H (300 MHz, $CDCl_3$): 3.88 (3H, s), 3.94 (9H, s), 5.63 (1H, s), 6.73 (2H, s), 6.86 (1H, d, J = 8.3), 6.89 (1H, d, J = 16.2), 6.95 (1H, d, J = 16.2), 6.99 (1H, dd, J = 8.3, 1.9), 7.16 (1H, d, J = 1.9). Further elution afforded 3,3′,4,4′,5,5′-hexamethoxybiphenyl[20] (**12**) as an orange solid (30 mg, 6%). mp 127−129 °C (lit. mp 128−130 °C).[20a] R_f = 0.45 (SiO_2 petrol: EtOAc 1:1). δ_H (300 MHz): 3.92 (6H, s), 3.96 (12H, s), 6.74 (4H, s).

Cis Combretastatin A-4 (1). (*E*)-3-(3′-Hydroxy-4′-methoxyphenyl)-2-(3″,4″,5″-trimethoxyphenyl)prop-2-enoic acid, **14**, (2 g, 5.56 mmol) was added to powdered copper (1.84 g, 28.8 mmol) in quinoline (20 mL, 21.9 g, 0.17 mol), and the resulting mixture was heated at 200 °C for 2 h. Upon cooling, ether was added, and the copper was filtered off through Celite. The filtrate was washed with 1 M hydrochloric acid, and the aqueous layer was separated and extracted with ether. The combined organic layers were washed with saturated aqueous sodium carbonate, water, brine, dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography (SiO_2 petrol: EtOAc 7:3) and recrystallization from ethyl acetate and petrol afforded cis combretastatin A-4 (**1**) as a pale yellow crystalline solid (1.19 g, 68%). mp 117−118 °C (lit. mp[6] 116 °C). Spectroscopic data were identical to that obtained previously. Elemental analysis of copper content: trace amounts detected (0.006%). Further elution afforded a mixture of the cis **1** and trans **3** stilbenes (182 mg, 10%).

Trans Combretastatin (3). To a solution of cis combretastatin A-4 (**1**) (200 mg, 0.63 mmol) in chloroform (10 mL) was added iodine (16 mg, 0.06 mmol, 10 mol %). The resulting solution was stirred at room temperature for 30 min, after which the solution was washed thoroughly with saturated aqueous sodium metabisulfite, destroying the remaining iodine. The yellow solution was washed with water, dried ($MgSO_4$), and concentrated in vacuo furnishing the *E* stilbene **3** as an off-white solid (198 mg, 99%). mp 102−104 °C (lit. mp[5c] 103−104 °C). Spectroscopic data were identical to that obtained previously.

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Supporting Information Available: Experimental results and characterization data for compounds **5**−**8**, **11**, **14**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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