Ethynylation of Aryl Halides by a Modified Suzuki Reaction: Application to the Syntheses of Combretastatin A-4, A-5 and Lunularic Acid

Alois Fürstner* and Katharina Nikolakis

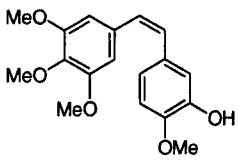
Max-Planck-Institut für Kohlenforschung,
Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany

Received July 11, 1996

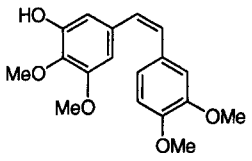
Key Words: Suzuki reaction / Organoboron compounds / Palladium catalysis / Chemo-therapeutic agents / Alkynes / Lunularic acid / Combretastatin

On treatment with trimethyl borate sodium acetylide undergoes a palladium-catalyzed cross coupling with functionalized aryl halides or triflates in reasonable to good yields. The ethynylarenes thus obtained serve as building blocks for the formation of the highly effective tubulin polymerization inhibitors combretastatin A-4 (**1**) and A-5 (**2**) as well as for the synthesis of the plant-growth regulator lunularic acid (**36**).

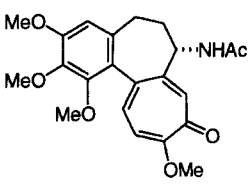
Tubulin as the major protein component of the microtubules constitutes a formidable target in search of anticancer chemotherapeutics. With the *Vinca* alkaloids[1] and quite recently with taxol[2], drugs binding to tubulin have already entered clinical use. Another very promising class of antineoplastic agents which affects this subcellular target is the combretastatin family, consisting of several closely related stilbene, phenanthrene and biphenyl derivatives isolated from the South African willow tree *Combretum caffrum*[3–5]. The most active among them is combretastatin A-4 (**1**), which is an exceptionally strong inhibitor of tubulin polymerization ($IC_{50} \approx 2-3$ μM) and belongs to the most cytotoxic agents tested so far against murine lymphocytic leukemia (L1210, P388; $ED_{50} \approx 0.003$ μM), human ovarian (A2780) and human colon cancer cell lines (e.g. HCT-15; $ED_{50} \approx 0.0009$ μM). The combretastatins share a common binding site on tubulin with the well-known antimitotic agents colchicine, podophyllotoxin and steganacin, but clearly surpass the latter compounds in activity[5]. The structural relationship, however, is obvious.



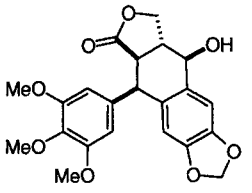
Combretastatin A-4 (**1**)



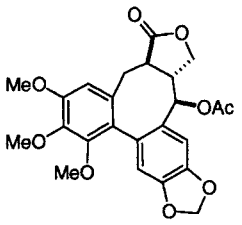
Combretastatin A-5 (**2**)



Colchicine



Podophyllotoxin



Steganacin

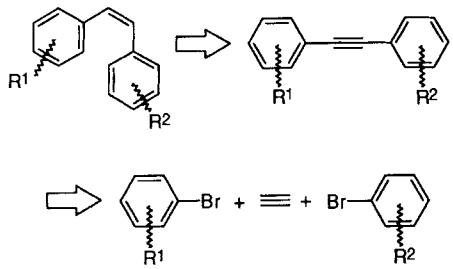
The simplicity of combretastatin A-4 offers promise for the rational design of new chemotherapeutic agents. Therefore, many efforts have been devoted to the detailed study of the structure-activity relationship of substituted stilbene derivatives of this type[5–7] as well as to the search for water-soluble prodrugs[6]. From these investigations it must be concluded (i) that only limited modifications in the substitution pattern of the arene rings can be made without compromising the cytotoxic activity, and (ii) that the (*Z*) configuration of the ethene bridge is essential.

The known synthetic approaches to combretastatin A-4 and analogues, however, do not well account for this latter feature. As they are based on Wittig reactions, mixtures of the (*Z*) and (*E*) isomers are inevitably formed which are difficult to separate on a preparative scale[3].

In the following we report on an alternative entry into this highly valuable class of compounds which avoids this problem and allows systematic variations of the arenes for further pharmacological studies. Our approach (Scheme 1) is based on the (*Z*)-selective Lindlar-type semihydrogenation of an appropriate alkyne precursor, which can be readily assembled by two consecutive Suzuki-type cross coupling reactions.

  0947–3440/96/1212–2107 $ 15.00+.25/0

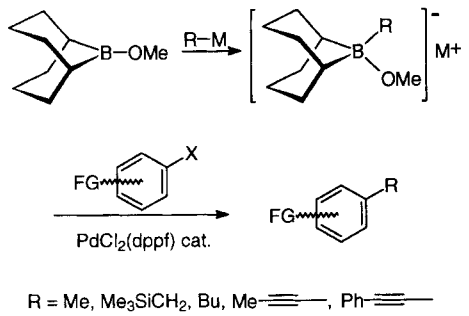
Scheme 1. Retrosynthetic analysis of (*Z*)-stilbene derivatives of the combretastatin series



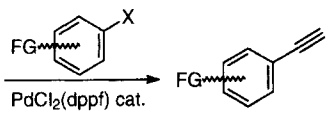
Preparation of Arylacetylenes by a Modified Suzuki Reaction

We recently disclosed a new protocol which extends the scope of the venerable Suzuki reaction[8,9]. It is based on the addition of a polar organometallic reagent R–M to 9-MeO–9-BBN leading to a well-defined borate complex that readily transfers its R group to an aryl–PdX complex formed by insertion of Pd^0 into a (functionalized) aryl halide. Reductive elimination of the resulting diorganopalladium species then affords the desired coupling product and regenerates the catalyst (Scheme 2)[9]. Although several substituted alkynyl metal reagents RC≡CM (R ≠ H) can be conveniently grafted on arenes by this method, attempts to transfer sodium acetylide itself (R = H) met with rather poor yields.

Scheme 2. Boron-mediated, palladium-catalyzed cross coupling of different polar organometallic reagents RM with aryl halides (X = Br, I) or triflates (X = OSO_2CF_3)

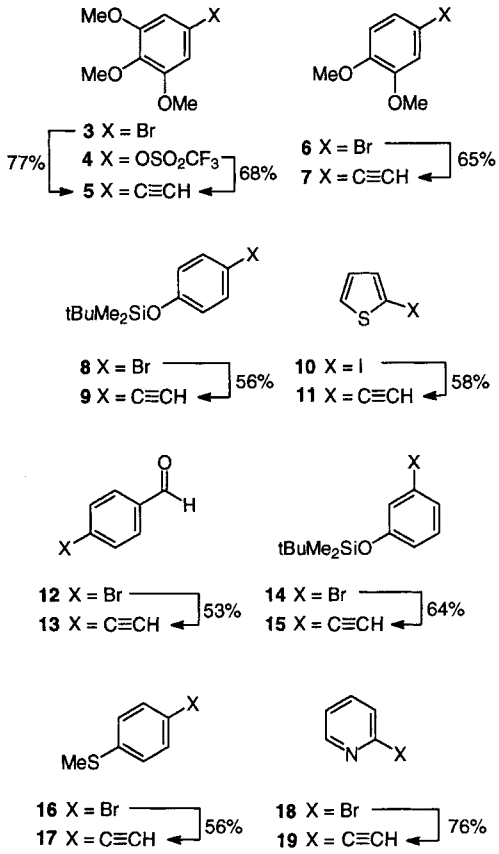


$HC{\equiv}CNa + B(OMe)_3 \longrightarrow [HC{\equiv}CNa \cdot B(OMe)_3]$



We now report that trimethyl borate [$B(OMe)_3$], however, as a substitute for 9-MeO–9-BBN serves this purpose very well[10]. Although the addition of sodium acetylide to $B(OMe)_3$ (1.5 equiv.) in THF leads to a mixture of borate complexes by ligand scrambling (denoted as [HC≡CNa · $B(OMe)_3$])[11], the subsequent reaction with an aryl halide in the presence of catalytic amounts of $PdCl_2$(dppf) [dppf = 1,1′-bis(diphenylphosphino)ferrocene][20] (3 mol-%) proceeds straightforwardly and gives the corresponding arylacetylene in reasonable to good yields. Some representative examples are compiled in Scheme 3 including those building blocks which are necessary for the approach to the combretastatins and related natural products (vide infra). However, it should be noted that substituted arylacetylenes of this type also serve as substrates for other purposes, such as polymerizations, hydroformylations, and for the preparation of materials with nonlinear optical properties, just to mention a few[12]. Aryl triflates can also be ethynylated in this way, provided that KBr is added to the reaction mixture in order to stabilize the intermediate arylpalladium species. As shown by the formation of compound **13**, even an aldehyde group is compatible if the solution of [HC≡CNa · $B(OMe)_3$] is slowly added to the reaction mixture.

Scheme 3. Palladium-catalyzed ethynylation of different aryl halides and triflates; conditions: $B(OMe)_3$ (1.5 equiv.), NaC≡CH (1 equiv.), aryl halide (0.8 equiv.), $PdCl_2$(dppf) (3 mol-%), THF, reflux



This procedure compares well with the current alternatives for the ethynylation of haloarenes[13–16]. Sodium acetylide as well as $B(OMe)_3$ are very cheap, commercially available, and of *no physiological concern*. Aiming at the synthesis of pharmaceutically relevant target molecules this may be a major advantage over the closely related Stille

coupling using tributylethynylstannane[13] as well as over ethynylations according to Sonogashira et al. (aryl halide, terminal alkyne, Et_2NH, CuI, Pd^0 cat.), which necessitate copper salts as additives[14]. Since this latter method does not afford terminal alkynes on reaction of aryl halides with acetylene gas[15], either 2-methyl-3-butyn-2-ol or, more appropriately, the rather expensive trimethylsilylethyne must be used as reagent, both of which require a subsequent deprotection step[14]. Finally, it should be noted that sodium acetylide is definitely among the cheapest acetylene anion equivalents in terms of price per mol.

Syntheses of Combretastatin A-4 and A-5

As shown in Scheme 4, the arylacetylene **5** can be stereoselectively converted into combretastain A-4 (**1**) in a few steps. Specifically, its 9-MeO−9-BBN-mediated Suzuki-type cross coupling[9a] with the bromide **21** [obtained by Baeyer-Villiger reaction of commercially available 5-bromo-2-methoxybenzaldehyde (**20**) and subsequent silylation of the resulting phenol] affords the tolane **23** in 70% yield after deprotection of the silyl ether **22**. Subsequent (*Z*)-selective semihydrogenation with a Lindlar catalyst (5% Pd/C, ethylenediamine) in MeOH provides combretastatin A-4 (**1**) in 80% yield together with a minor amount of the corresponding alkane **25** (R = H) (GC: **1**/**25** = 86:14). The latter, however, can only be removed by preparative HPLC. Therefore, it is more convenient to hydrogenate compound **22** with the silyl group still in place, since the stilbene **24** can be separated from the corresponding alkane **25** (R = $SiMe_2tBu$) by simple flash chromatography. Final deprotection of **24** with aq. tetra-*n*-butylammonium fluoride (TBAF) in EtOAc leads to combretastatin A-4 (**1**) in high yield.

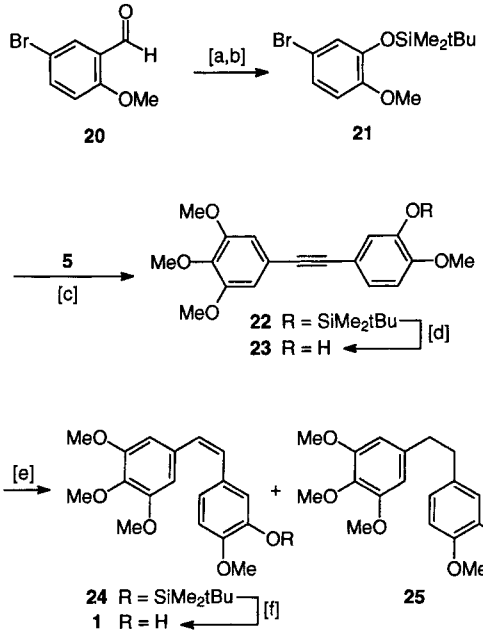
In close analogy, combretastatin A-5 (**2**) can be prepared from the acetylene derivative **7** and the bromoarene **27** by means of a 9-MeO−9-BBN mediated cross coupling[9a] as the key step (Scheme 5). The latter substrate is well accessible from the commercially available aldehyde **26** in three simple steps. Lindlar hydrogenation of **28a** as described above, followed by flash-chromatographical separation of a minor amount of the overreduced product **30** gave the pure (*Z*)-alkene **29** in 72% yield, which was deprotected to combretastatin A-5 (**2**) with aq. TBAF as usual.

As exemplified by these sequences, valuable antineoplastic natural products of the combretastatin A series can be readily prepared in stereochemically pure form without need for the separation of isomers. It is obvious that this convergent approach is well suited for the formation of hitherto unknown combretastatin analogues in search of drugs with an even better pharmacological profile.

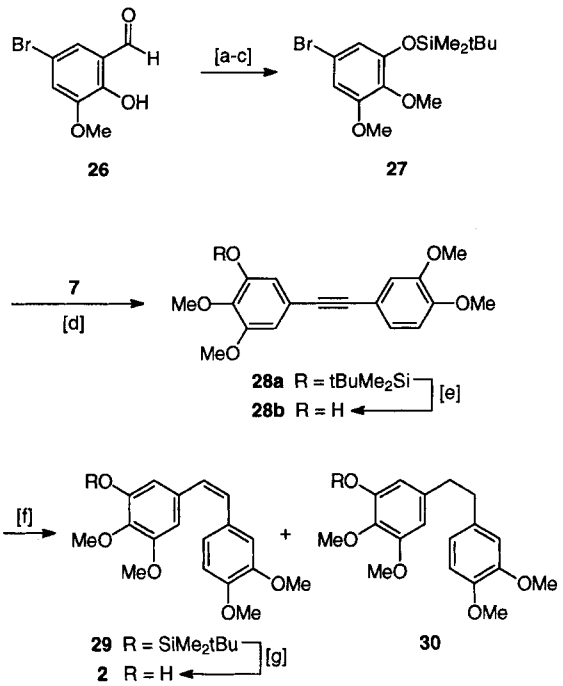
Synthesis of Lunularic Acid

The dihydrostilbene derivative lunularic acid (**36**) was first isolated as a dormancy factor from *Lunularia cruciata* and later on detected in *Marchantia polymorpha* and more than 70 other species of liverworts and algae[17]. The content of **36** in plant material is controlled by a phytochrome-mediated day-length response and its prime action consists in the regulation/inhibition of the growth of the plant.

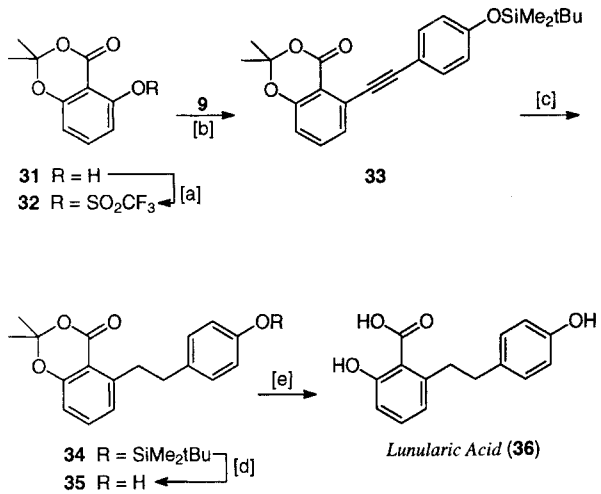
Scheme 4. Synthesis of combretastatin A-4 (**1**): [a] MCPBA, CH_2Cl_2, 86%; [b] TBDMSCl, imidazole, THF, 83%; [c] lithiated **5** (*n*BuLi, THF), 9-MeO−9-BBN, $PdCl_2$(dppf) (3 mol-%); [d] aq. TBAF, EtOAc, 70% both steps; [e] H_2 (1 atm), Pd/C (5% w/w), ethylenediamine, MeOH, 74% (see text); [f] aq. TBAF, EtOAc, 95%



Scheme 5. Synthesis of combretastatin A-5 (**2**): [a] Me_2SO_4, K_2CO_3, acetone, 77%; [b] *m*-chloroperbenzoic aicd, CH_2Cl_2, 78%; [c] TBDMSCl, imidazole, THF, 92%; [d] lithiated **7** (*n*BuLi, THF), 9-MeO−9-BBN, $PdCl_2$(dppf) (3 mol-%); [e] aq. TBAF, EtOAc, 72% for both steps; [f] Pd/C (5% w/w), ethylenediamine, MeOH, H_2 (1 atm), 72%; [g] aq. TBAF, EtOAc, 93%



Scheme 6. Synthesis of lunularic acid (**36**): [a] triflic anhydride, pyridine, 91%; [b] lithiated **9** (*n*BuLi, THF), 9-MeO–9-BBN, KBr (1.4 equiv.), $PdCl_2$(dppf) (3 mol-%), 73%; [c] H_2 (1 atm), Pd/C (5%, w/w), MeOH, 94%; [d] TBAF, EtOAc, 96%, [e] aq. KOH, DMSO, 80°C, 90%



Our synthesis of this metabolite (Scheme 6) starts with commercially available 2,6-dihydroxybenzoic acid, which was protected as acetonide **31** according to a literature procedure[18]. The remaining phenolic hydroxy group was converted into the corresponding triflate **32**, which was cross-coupled in the presence of KBr by means of our 9-MeO–9-BBN-based method[9a] with the lithium anion of the phenylacetylene derivative **9** in 73% isolated yield. Hydrogenation of the resulting alkyne **33** followed by deprotection of the silyl ether and of the acylal-like 1,3-dioxane group afforded lunularic acid (**36**) in high overall yield.

Financial support by the *Fonds der Chemischen Industrie* is gratefully acknowledged.

Experimental

All reactions were carried out under Ar by using Schlenk techniques. – NMR: Bruker AC 200 spectrometer, 200.1 MHz (^{1}H) and 50.3 MHz (^{13}C) in $CDCl_3$ (Aldrich) unless stated otherwise, internal standard TMS, coupling constants (*J*) in Hz. The multiplicity in the ^{13}C-NMR spectra refers to the geminal protons (DEPT). – MS: Varian CH-5 (70 eV). – IR: Nicolet FT-7199. – Raman: CODERG, LRT 800 Laser Spectra Physics, argon ion laser (4880 Å), krypton ion laser (6471 Å). – Melting points: Gallenkamp apparatus (uncorrected). – Elemental Analyses: Dornis und Kolbe, Mülheim. – 9-MeO–9-BBN was prepared from [9-H–9-BBN]$_2$ and MeOH according to a literature procedure[19]. $B(OMe)_3$ (Aldrich) was distilled prior to use. The haloarenes and $PdCl_2$(dppf)[20] were purchased from Aldrich Chemical Co. and used as received. Sodium acetylide (Aldrich, 95%, 18% suspension in mineral oil) was thoroughly washed with pentane in order to remove the mineral oil and then dried in vacuo. – Flash chromatography: Merck silica gel 60 (230–400 mesh) using hexane/EtOAc in various proportions as eluent. – The THF used was dried by distillation over Mg-anthracene and transferred under Ar.

Representative Procedure for the Palladium-Catalyzed Cross Coupling of Sodium Acetylide with Aryl Halides Mediated by $B(OMe)_3$. – 5-Ethynyl-1,2,3-trimethoxybenzene (**5**): To a suspension of sodium acetylide (262 mg, 5.46 mmol) in THF (20 ml), $B(OMe)_3$ (825 mg, 7.94 mmol) was added causing rapid dissolution. $PdCl_2$(dppf) (107 mg, 0.13 mmol) and 5-bromo-1,2,3-trimethoxybenzene (**3**) (1.078 g, 4.365 mmol) were then added and the mixture was refluxed for 27 h. For work-up, the reaction was quenched with water (20 ml), the aqueous layer was twice extracted with hexane (30 ml each), the combined organic layers were dried with Na_2SO_4 and the solvent was evaporated in vacuo. Flash chromatography (hexane/ethyl acetate, 4:1 → 2:1) of the crude product afforded the title compound as colorless crystals (645 mg, 77%); m.p. 70–71°C (ref.[21a] 68–68.5°C). – IR: $\tilde{\nu}$ = 3272 cm^{-1}, 3093, 2987, 2964, 2939, 2826, 1579, 1503, 1467, 1457, 1431, 1410, 1339, 1298, 1233, 1181, 1135, 1005, 958, 833, 777, 697, 628. – ^{1}H NMR: δ = 6.73 (s, 2H), 3.86, 3.85 (2 s, 9H), 3.30 (s, 1H). – ^{13}C NMR: δ = 152.7 (s), 139.0 (s), 116.7 (s), 109.0 (d), 83.3 (d), 75.9 (s), 60.6 (q), 55.8 (q). – MS; *m/z* (%): 192 (100) [M$^+$], 177 (59), 149 (13), 134 (14), 117 (12).

The same product (346 mg, 68%) was obtained by reaction of triflate **4** (832 mg, 2.63 mmol) with HC≡CNa (158 mg, 3.29 mmol), $B(OMe)_3$ (541 mg, 5.21 mmol), $PdCl_2$(dppf) (64 mg). In this case KBr (441 mg, 3.71 mmol) must be added to the reaction mixture in order to stabilize the intermediate arylpalladium species.

All other products shown in Scheme 3 were obtained analogously. Their analytical data are compiled below.

4-Ethynyl-1,2-dimethoxybenzene[21d] (**7**): 65%; m.p. 71–72°C. – IR: $\tilde{\nu}$ = 3251 cm^{-1}, 2970, 2939, 2843, 1597, 1579, 1511, 1452, 1408, 1323, 1263, 1240, 1152, 1138, 1025, 860, 821, 810, 729. – ^{1}H NMR: δ = 7.08 (dd, 1H, *J* = 2, 8), 6.97 (d, 1H, *J* = 2), 6.78 (d, 1H, *J* = 8), 3.87 (s, 3H), 3.85 (s, 3H), 2.98 (s, 1H). – ^{13}C NMR: δ = 149.5 (s), 148.2 (s), 125.1 (d), 114.4 (d), 113.9 (s), 110.6 (d), 83.4 (d), 75.3 (s), 55.5 (q). – MS; *m/z* (%): 162 (100) [M$^+$], 147 (31), 119 (14), 91 (31), 76 (16), 65 (21), 50 (11). – HRMS ($C_{10}H_{10}O_2$): calcd. 162.0681; found 162.0686.

4-(tert-Butyldimethylsilyloxy)-1-ethynylbenzene[12d] (**9**): Syrup (56%). – IR: $\tilde{\nu}$ = 3318 cm^{-1}, 3296, 3041, 2957, 2931, 2887, 2859, 2109, 1603, 1505, 1472, 1464, 1265, 1165, 1099, 912, 840, 809, 782. – ^{1}H NMR: δ = 7.35 and 6.76 (AB system, 4H, *J* = 8.5), 2.97 (s, 1H), 0.96 (s, 9H), 0.18 (s, 6H). – ^{13}C NMR: δ = 156.0, 133.2, 119.8, 114.6, 83.4, 75.6, 25.3, 17.9, –4.8. MS; *m/z* (%): 232 (19) [M$^+$], 175 (100).

2-Ethynylthiophene[13] (**11**): Work-up by bulb-to-bulb distillation (b.p. 30–32°C/13 Torr). – Syrup (58%). – IR: $\tilde{\nu}$ = 3295 cm^{-1}, 3108, 2105, 1420, 1228, 1146, 1130, 1040, 852, 834, 704, 682, 664, 601, 568. – ^{1}H NMR: δ = 7.26–7.31 (m, 2H), 6.96–7.01 (m, 1H), 3.35 (s, 1H). – ^{13}C NMR: δ = 132.7, 127.2, 126.5, 121.7, 80.9, 76.7. – MS; *m/z* (%): 108 (100) [M$^+$], 82 (11), 69 (28), 58 (21), 45 (17).

4-Ethynylbenzaldehyde[14b] (**13**): In this case the solution of [HC≡CNa · $B(OMe)_3$] in THF was slowly added over a period of 24 h to the solution of 4-bromobenzaldehyde (**12**) and the palladium catalyst in THF. Work-up as described afforded the title compound as pale-yellow crystals (53%); m.p. 85–86°C (ref.[14b] 88–90°C). – IR: $\tilde{\nu}$ = 3293 cm^{-1}, 3220, 2838, 2741, 2101, 1703, 1687, 1606, 1562, 1390, 1364, 1305, 1289, 1208, 1165, 848, 830, 741, 729, 682, 530. – ^{1}H NMR: δ = 9.99 (s, 1H), 7.81 and 7.61 (AB system, 4H, *J* = 8), 3.27 (s, 1H). – ^{13}C NMR: δ = 191.4, 136.0, 132.7, 129.5, 128.3, 82.7, 81.1. – MS; *m/z* (%): 130 (100) [M$^+$], 129 (95), 101 (65), 75 (24), 74 (13), 51 (18), 50 (11).

3-(tert-Butyldimethylsilyloxy)-1-ethynylbenzene[12d] (**15**): Syrup (64%). – IR: $\tilde{\nu}$ = 3298 cm^{-1}, 3069, 3030, 2957, 2931, 2887, 2859, 2108, 1595, 1576, 1478, 1464, 1417, 1391, 1362, 1282, 1257, 1148, 1003, 967, 879, 839, 784, 688, 647, 607. – ^{1}H NMR: δ = 7.06–7.28

(m, 2H), 6.96–6.98 (m, 1H), 6.83 (ddd, 1H, J = 1.5, 2.5, 12), 3.03 (s, 1H), 0.99 (s, 9H), 0.20 (s, 6H). – ^{13}C NMR: δ = 155.1, 129.0, 125.0, 123.3, 122.8, 120.8, 83.2, 76.7, 25.3, 17.8, –4.8. – MS; *m/z* (%): 232 (19) [M$^+$], 176 (22), 175 (100).

1-Ethynyl-4-(methylthio)benzene[21b] (**17**): Work-up by bulb-to-bulb distillation (b.p. 35–37 °C/0.013 Torr). – Syrup (56%). – IR: ṽ = 3288, 2921, 2106, 1594, 1489, 1436, 1398, 1090, 820, 658, 616, 529 cm^{-1}. – ^{1}H NMR: δ = 7.40 and 7.18 (AB, 4H, J = 8.6), 3.06 (s, 1H), 2.46 (s, 3H). – ^{13}C NMR: δ = 139.7, 132.0, 125.4, 118.0, 83.1, 76.9, 14.9. – MS; *m/z* (%): 148 (100) [M$^+$], 133 (27), 115 (9), 102 (12), 89 (38).

2-Ethynylpyridine[14d] (**19**): Syrup (76%). – IR: ṽ = 3293 cm^{-1}, 3215, 3053, 3005, 2110, 1583, 1562, 1462, 1428, 1286, 1244, 1214, 1151, 1091, 1045, 991, 780, 740, 658, 629, 538. – ^{1}H NMR: δ = 8.60–8.62 (m, 1H), 7.67 (dt, 1H, J = 2, 8), 7.49 (td, 1H, J = 1, 8), 7.28 (ddd, 1H, J = 1, 5, 8), 3.16 (s, 1H). – ^{13}C NMR: δ = 149.9, 142.2, 136.0, 127.3, 123.2, 108.2, 77.0. – MS; *m/z* (%): 103 (100) [M$^+$], 76 (39), 51 (14), 50 (30).

5-Bromo-1-(tert-butyldimethylsilyloxy)-2-methoxybenzene (**21**): To a solution of 5-bromo-2-methoxybenzaldehyde (**20**) (1.206 g, 5.608 mmol) in CH_2Cl_2 (20 ml), MCPBA (2.45 g, 14.2 mmol) was added and the mixture was stirred at ambient temperature for 2 d. The reaction was quenched with a sat. aq. $NaHCO_3$ solution, the aqueous phase was extracted with Et_2O (3 × 30 ml), the combined organic layers were dried with Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography (hexane/EtOAc, 4:1 → 2:1) affording 5-bromo-2-methoxyphenol as colorless crystals (0.98 g, 86%); m.p. 61–62 °C (ref.[21c] 60–62 °C). – IR: ṽ = 3479 cm^{-1}, 3405, 2974, 2939, 2841, 1593, 1500, 1454, 1436, 1333, 1289, 1263, 1223, 1174, 1127, 1025, 856, 798. – ^{1}H NMR: δ = 7.08 (d, 1H, J = 2), 6.98 (dd, 1H, J = 2, 8.6), 6.72 (d, 1H, J = 8.6), 5.65 (s, 1H, OH), 3.87 (s, 3H). – ^{13}C NMR: δ = 146.2, 145.5, 122.4, 117.5, 112.9, 111.5, 55.7. – MS; *m/z* (%): 204 (93) [M$^+$], 202 (100) [M$^+$], 189 (83), 187 (86), 161 (38), 159 (41), 79 (14), 63 (12), 51 (36). – This phenol (265 mg, 1.30 mmol), dissolved in THF (20 ml), was allowed to react overnight with imidazole (154 mg, 2.26 mmol) and TBDMSCl (205 mg, 1.36 mmol) at ambient temperature. For work-up the solution was diluted with hexane, successively washed with NaOH (5%, 20 ml), water and brine (20 ml each), the organic layer was dried with Na_2SO_4, concentrated, and the crude product purified by flash chromatography (hexane/EtOAc, 4:1 → 2:1) affording compound **21** as a colorless syrup (345 mg, 83%)[6d]. – IR: ṽ = 2955 cm^{-1}, 2930, 2897, 2858, 1585, 1500, 1472, 1463, 1442, 1402, 1303, 1270, 1225, 1180, 1133, 1032, 935, 864, 832, 785. – ^{1}H NMR: δ = 6.95–7.03 (m, 2H), 6.69 (d, 1H, J = 8.4), 3.76 (s, 3H), 0.97 (s, 9H), 0.14 (s, 6H). – ^{13}C NMR: δ = 150.1, 145.6, 124.1, 123.7, 112.9, 112.0, 55.2, 25.3, 18.1, –5.0. – MS; *m/z* (%): 318, 316 (4) [M$^+$], 261 (80), 259 (79), 246 (100), 244 (99), 231 (19), 229 (18), 216 (10), 214 (10), 73 (12), 59 (10).

Alkynes **22** *and* **23**: To a solution of substrate **5** (65 mg, 0.34 mmol) in THF (10 ml) *n*BuLi (1.6 M in hexane, 0.25 ml, 0.40 mmol) was added at –78 °C. 9-MeO–9-BBN (75 mg, 0.49 mmol) was then introduced, the resulting solution was allowed to warm to ambient temperature, $PdCl_2$(dppf) (8 mg, 0.01 mmol) and bromide **21** (107 mg, 0.34 mmol) were added, and the mixture was refluxed for 15 h. A standard extractive work-up followed by flash chromatography with hexane/EtOAc (10:1→4:1→1:2) afforded compound **22** as colorless crystals; m.p. 81–82 °C. – IR: ṽ = 3003 cm^{-1}, 2954, 2933, 2858, 1577, 1511, 1467, 1412, 1359, 1302, 1265, 1237, 1209, 1176, 1135, 1112, 1024, 1002, 950, 874, 836, 806, 783. – Raman: ṽ = 2216 cm^{-1}, 1600, 1590, 1300, 1290, 1110. – ^{1}H NMR: δ = 7.10 (dd, 1H, J = 1.9, 8.3), 7.00 (d, 1H, J = 1.9), 6.78 (d, 1H, J = 8.3), 6.73 (s, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 3.80 (s, 3H), 0.99 (s, 9H), 0.15 (s, 6H). – ^{13}C NMR: δ = 153.1 (s), 151.7 (s), 144.8 (s), 138.6 (s), 125.8 (d), 124.0 (d), 118.6 (s), 115.3 (s), 111.8 (d), 108.7 (d), 88.5 (s), 87.8 (s), 61.0 (q), 56.2 (q), 55.4 (q), 25.7 (q), 18.5 (s), –4.6 (s). – MS; *m/z* (%): 428 (33) [M$^+$], 371 (37), 356 (100), 341 (30), 178 (25), 149 (11). – HRMS ($C_{24}H_{32}SiO_5$): calcd. 428.2019; found 428.2018. – $C_{24}H_{32}SiO_2$ (428.6): calcd. C 67.26, H 7.53, Si 6.55; found C 67.08, H 7.58, Si 6.47. – This product, dissolved in EtOAc (5 ml), was desilylated by reaction with aq. TBAF (70%, 0.5 ml) for 10 min. Standard work-up followed by flash chromatography with hexane/EtOAc (2:1→1:1) provided the alkyne **23** as a colorless syrup (75 mg, 70%). – IR: ṽ = 3439 cm^{-1}, 2926, 2854, 1576, 1511, 1462, 1410, 1357, 1280, 1248, 1237, 1127, 1025. – ^{1}H NMR: δ = 7.06–7.10 (m, 1H), 7.02 (d, 1H, J = 1.9), 6.79 (d, 1H, J = 8), 6.73 (s, 2H), 5.70 (br. s, 1H, OH), 3.88 (s, 3H), 3.85 (s, 6H), 3.84 (s, 3H). – ^{13}C NMR: δ = 153.1, 147.1, 145.4, 138.7, 124.2, 118.6, 117.6, 117.5, 116.0, 110.6, 110.4, 108.9, 108.7, 88.5, 87.9, 61.1, 60.8, 56.1, 55.8. – MS; *m/z* (%): 314 (100) [M$^+$], 299 (75), 271 (13), 157 (12). – HRMS ($C_{18}H_{18}O_5$): calcd. 314.1154; found 314.1145.

tert-Butyldimethylsilyl Ether of Combretastatin A-4 (**24**): Alkyne **22** (100 mg, 0.233 mmol), dissolved in MeOH (10 ml), was hydrogenated (H_2, 1 atm) over a Lindlar catalyst, prepared from Pd/C (5% w/w, 1.5 mg) and ethylenediamine (14 mg), the hydrogen uptake being monitored by a gas burette. After 25 min, the catalyst was filtered off and the filtrate was worked up as usual. Flash chromatography of the crude product with hexane/EtOAc (10:1) gave **24** as a colorless syrup (74 mg, 74%)[3b]. – IR: ṽ = 2999 cm^{-1}, 2956, 2931, 2858, 1579, 1509, 1464, 1425, 1327, 1282, 1237, 1130, 1010, 963, 888, 843, 784, 733. – ^{1}H NMR: δ = 6.69–6.85 (m, 3H), 6.48 (s, 2H), 6.42 (d, 2H, J = 12), 3.81 (s, 3H), 3.76 (s, 3H), 3.68 (s, 6H), 0.91 (s, 9H), 0.39 (s, 6H). – ^{13}C NMR: δ = 153.0, 150.3, 144.7, 137.1, 133.1, 130.1, 129.7, 128.8, 122.9, 121.3, 111.7, 106.0, 60.9, 55.9, 55.5, 25.7, 18.4, –4.7. – MS; *m/z* (%): 430 (43) [M$^+$], 375 (14), 373 (28), 358 (100), 343 (30). – $C_{24}H_{34}O_5Si$ (430.6): calcd. C 66.94, H 7.96; found C 66.90, H 7.85.

Combretastatin A-4 (**1**): To a solution of the silyl ether **24** (70 mg, 0.16 mmol) in EtOAc (5 ml), TBAF (70% in water, 1 ml) was added. After 30 min, the mixture was diluted with water, the aqueous phase was extracted with EtOAc in several portions, the combined organic layers were dried (Na_2SO_4), the solvent was evaporated, and the residue chromatographed (hexane/EtOAc 4:1→2:1) to afford **1** (49 mg, 95%), the spectral data of which are identical with those reported in ref.[3]. – IR: ṽ = 3425 cm^{-1}, 3003, 2938, 2837, 1614, 1580, 1509, 1461, 1419, 1328, 1275, 1238, 1182, 1127, 1027, 1006, 881, 855, 795, 762. – ^{1}H NMR: δ = 6.93 (d, 1H, J = 2), 6.76 (dd, 1H, J = 2, 8.4), 6.74 (d, 1H, 8.4), 6.53 (s, 2H), 6.47 and 6.42 (AB, 2H, J = 12.2), 5.58 (br. s, 1H, OH), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (s, 6H). – ^{13}C NMR: δ = 152.9, 145.8, 145.3, 137.2, 132.7, 130.7, 129.5, 129.1, 121.1, 115.1, 110.4, 106.1, 60.9, 56.0. – MS; *m/z* (%): 316 (100) [M$^+$], 301 (74).

5-Bromo-1-(tert-butyldimethylsilyloxy)-2,3-dimethoxybenzene (**27**): To a mixture of 5-bromo-2-hydroxy-3-methoxybenzaldehyde (1.55 g, 6.70 mmol) and K_2CO_3 (3.1 g, 22.4 mmol) in acetone (100 ml), dimethyl sulfate (1.26 g, 10.0 mmol) was added. The mixture was refluxed for 3 h, the solvent was removed in vacuo, the residue dissolved in water and the aqueous layer repeatedly extracted with EtOAc. The combined organic phases were dried (Na_2SO_4), the solvent was evaporated and the crude product purified by flash chromatography (hexane/EtOAc, 10:1→4:1) affording 5-bromo-2,3-dimethoxybenzaldehyde as colorless crystals (1.27 g, 77%); m.p. 65.5–66.5 °C. – IR: ṽ = 3082 cm^{-1}, 2967, 2941, 2890, 2843, 1680,

1578, 1484, 1446, 1430, 1395, 1318, 1269, 1244, 1219, 1075, 991, 932, 854, 688, 583, 551. – ^{1}H NMR: δ = 10.34 (s, 1H), 7.51 (d, 1H, *J* = 2.5), 7.23 (d, 1H), 3.97 (s, 3H), 3.91 (s, 3H). – ^{13}C NMR: δ = 188.2 (d), 153.5 (s), 151.5 (s), 130.1 (s), 121.3 (d), 120.6 (d), 116.6 (s), 62.0 (q), 55.9 (q). – MS; *m/z* (%): 246 (100), 231 (24), 229 (28) [M$^+$ – Br], 228 (28), 226 (23), 217 (15), 215 (14), 200 (24), 198 (23), 188 (13), 186 (12), 148 (11), 108 (14), 94 (35), 79 (15). – To a solution of this compound (167 mg, 0.68 mmol) in CH_2Cl_2 (20 ml), MCPBA (300 mg, 1.74 mmol) was added and the mixture was refluxed for 2 d. Quenching of the reaction with a saturated $NaHCO_3$ solution, followed by a standard extractive work-up and flash chromatography (hexane/EtOAc, 5:1) gave 5-bromo-2,3-dimethoxyphenol (124 mg, 78%) as a colorless syrup, which exhibits the following spectral properties: IR: ν̃ = 3410 cm^{-1}, 3013, 2968, 2952, 2838, 1594, 1497, 1465, 1438, 1427, 1336, 1318, 1233, 1205, 1163, 1112, 989, 982, 961, 852, 827, 807, 762, 729. – ^{1}H NMR: δ = 6.75 (d, 1H, *J* = 2.4), 6.59 (d, 1H), 5.27 (br. s, 1H, OH), 3.85 (s, 3H), 3.82 (s, 3H). – ^{13}C NMR: δ = 152.5, 149.6, 134.0, 116.0, 111.3, 107.6, 60.6, 55.7. – MS; *m/z* (%): 234, 232 (100) [M$^+$], 219 (81), 217 (83), 191 (32), 189 (35), 176 (18), 174 (21), 110 (16), 67 (21), 53 (15), 39 (21). Silylation of this phenol derivative (145 mg, 0.62 mmol) with TBDMSCl (187 mg, 1.24 mmol) and imidazole (85 mg, 1.2 mmol) in THF at room temp., followed by flash chromatography of the crude product (hexane/EtOAc, 4:1→2:1) gave **27** as a colorless syrup (198 mg, 92%). – IR: ν̃ = 2956 cm^{-1}, 2932, 2858, 1583, 1490, 1412, 1319, 1252, 1219, 1175, 1118, 1008, 989, 866, 832, 784. – ^{1}H NMR: δ = 6.61 and 6.55 (AB, 2H, *J* = 2.3), 3.75 (s, 3H), 3.68 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H). – ^{13}C NMR: δ = 153.9 (s), 149.9 (s), 139.8 (s), 117.1 (d), 115.2 (s), 108.9 (d), 60.0 (q), 55.8 (q), 25.3 (q), 17.9 (s), –5.1 (q). – MS; *m/z* (%): 348, 346 (3) [M$^+$], 291 (64), 289 (64), 276 (95), 274 (100), 233 (11), 231 (14), 73 (19). – $C_{14}H_{23}BrO_3Si$ (347.3): calcd. C 48.41, H 6.67; found C 48.73, H 6.63.

Alkyne **28a**: To a solution of alkyne **7** (50 mg, 0.3 mmol) in THF, *n*BuLi (1.6 M in hexane, 0.22 ml, 0.35 mmol) was added at –78 °C. After 30 min at that temperature, 9-MeO–9-BBN (58 mg, 0.38 mmol) was added and the mixture allowed to warm up. When ambient temp. was reached, $PdCl_2$(dppf) (8 mg, 0.01 mol) and bromide **27** (117 mg, 0.34 mmol) were added and the mixture was refluxed for 17 h. Work-up as described above afforded **28a** as a colorless syrup. – IR: ν̃ = 2999 cm^{-1}, 2955, 2934, 2903, 2857, 2838, 1589, 1570, 1515, 1464, 1413, 1365, 1245, 1227, 1171, 1137, 1118, 1026, 1007, 836, 816, 784. – ^{1}H NMR: δ = 6.93 (dd, 1H, *J* = 1.9, 8.2), 6.83 (d, 1H, *J* = 1.9), 6.62 (d, 1H, *J* = 8.2), 6.52 and 6.48 (AB, 2H, *J* = 2), 3.70 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H), 3.60 (s, 3H), 0.82 (s, 9H), 0.03 (s, 6H). – ^{13}C NMR: δ = 153.6, 149.5, 149.4, 148.7, 141.3, 124.9, 118.3, 117.6, 115.5, 114.3, 111.1, 108.9, 88.4, 87.9, 60.5, 56.0, 55.9, 25.7, 18.3, –4.6. – MS; *m/z* (%): 428 (19) [M$^+$], 371 (24), 356 (100), 178 (24). – HRMS ($C_{24}H_{32}O_5Si$): calcd. 428.2019, found 428.2016.

tert-Butyldimethylsilyl Ether of Combretastatin A-5 (**29**): A solution of alkyne **28a** (80 mg, 0.19 mmol) in MeOH (10 ml) was hydrogenated (H_2, 1 atm) over a Lindlar catalyst prepared from Pd/C (5% w/w, 1.2 mg) and ethylendiamine (12 µl). The hydrogen uptake was monitored by a gas burette. The catalyst was filtered off and the filtrate was worked up as usual affording **29** as a colorless syrup (58 mg, 72%)[13b] after flash chromatography with hexane/EtOAc (4:1→2:1) as eluent. – IR: ν̃ = 3000 cm^{-1}, 2954, 2934, 2902, 2857, 1574, 1513, 1500, 1464, 1424, 1336, 1257, 1238, 1117, 1028, 1010, 872, 838, 784. – Raman: ν̃ = 2209 cm^{-1}. – ^{1}H NMR: δ = 6.64–6.77 (m, 3H), 6.42 and 6.31 (AB, 2H, *J* = 12), 6.40 and 6.33 (AB, 2H, *J* = 1.9), 3.83 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.65 (s, 3H), 0.93 (s, 9H), 0.07 (s, 6H). – ^{13}C NMR: δ = 153.3, 149.2, 148.4, 148.1, 139.5, 132.9, 130.0, 129.6, 128.9, 121.7, 114.6, 111.8, 110.9, 106.1, 60.3, 55.8, 55.5, 25.6, 18.2, –4.8. – MS; *m/z* (%): 430 (47) [M$^+$], 373 (26), 358 (100), 343 (29), 163 (16).

Combretastatin A-5 (**2**): A solution of **29** (47 mg, 0.11 mmol) in EtOAc (5 ml) containing TBAF (70% in water, 1 ml) was stirred overnight. A standard extractive work-up followed by flash chromatography with hexane/EtOAc (4:1→2:1) gave **2** as a colorless syrup (32 mg, 93%). – IR: ν̃ = 3430 cm^{-1}, 3003, 2936, 2836, 1600, 1582, 1512, 1463, 1429, 1338, 1259, 1237, 1200, 1141, 1105, 1026, 1002, 871, 816, 793, 769. – ^{1}H NMR: δ = 6.71–6.86 (m, 3H), 6.57 (d, 1H, *J* = 2), 6.48 and 6.42 (AB, 2H, *J* = 12.1), 6.41 (d, 1H, *J* = 2), 5.68 (br. s, 1H, OH), 3.79 (s, 3H), 3.78 (s, 3H), 3.60 (s, 3H), 3.59 (s, 3H). – ^{13}C NMR: δ = 152.0, 149.1, 148.4, 148.3, 134.6, 133.6, 129.8, 128.6, 122.0, 111.9, 110.9, 108.7, 104.9, 61.0, 55.9, 55.7, 55.6. – MS; *m/z* (%): 316 (100) [M$^+$], 301 (14), 283 (18), 269 (8), 255 (9), 240 (8), 151 (12), 142 (11).

5-{2-[4-(tert-Butyldimethylsilyloxy)phenyl]ethynyl}-2,2-dimethylbenzo[1,3]dioxin-4-one (**33**): To a solution of alkyne **9** (213 mg, 0.92 mmol) in THF (10 ml), *n*BuLi (1.6 M in hexane, 0.62 ml, 1.0 mmol) was added at –78 °C. The mixture was stirred at this temperature for 30 min prior to the addition of 9-MeO–9-BBN (171 mg, 1.12 mmol). After warming to room temp., KBr (157 mg, 1.32 mmol), $PdCl_2$(dppf) (27 mg) and triflate **32** (359 mg, 1.10 mmol) were added and the mixture was refluxed for 3 h. A standard extractive work-up followed by flash chromatography with hexane/EtOAc (10:1→4:1) afforded **33** as colorless crystals (272 mg, 73%); m.p. 124–125 °C. – IR: ν̃ = 3078 cm^{-1}, 2991, 2954, 2929, 2894, 2858, 2214, 1741, 1592, 1578, 1507, 1472, 1329, 1273, 1256, 1207, 1166, 1045, 899, 850, 786, 691. – Raman: ν̃ = 2217 cm^{-1}. – ^{1}H NMR: δ = 7.36 (d, 2H, *J* = 8.6), 7.28 (t, 1H, *J* = 8), 7.12 (d, 1H, *J* = 8), 6.72 (d, 1H, *J* = 8), 6.65 (d, 2H, *J* = 8.6), 1.56 (s, 6H), 0.82 (s, 9H), 0.07 (s, 6H). – ^{13}C NMR: δ = 159.0, 156.6, 134.8, 133.6, 128.2, 126.8, 125.8, 120.5, 120.3, 116.7, 115.8, 105.6, 96.7, 86.8, 25.8, 25.7, 18.3, –4.4. – MS; *m/z* (%): 408 (45) [M$^+$], 350 (100), 293 (85). – HRMS ($C_{24}H_{28}O_4Si$): calcd. 408.1757; found 408.1753. – $C_{24}H_{28}O_4Si$ (408.6): calcd. C 70.55, H 6.91, Si 6.87; found C 70.42, H 6.92, Si 6.75.

5-{2-[4-(tert-Butyldimethylsilyloxy)phenyl]ethyl}-2,2-dimethylbenzo[1,3]dioxin-4-one (**34**): Alkyne **33** (360 mg, 0.87 mmol) dissolved in MeOH (10 ml) was hydrogenated (H_2, 1 atm) over Pd/C (5% w/w, ca. 5 mg) for 30 min, the catalyst was filtered off, the solvent was evaporated and the residue passed through a short pad of silica with hexane/EtOAc (4:1→2:1) as eluent affording **34** as colorless crystals (341 mg, 94%). – IR: ν̃ = 3088 cm^{-1}, 3030, 2995, 2954, 2926, 2892, 2855, 1732, 1606, 1581, 1508, 1478, 1445, 1388, 1312, 1275, 1224, 1170, 1050, 926, 905, 839, 808, 783. – ^{1}H NMR: δ = 7.33 (t, 1H, *J* = 8), 7.06 (d, 2H, *J* = 8.5), 6.69–6.82 (m, 4H), 3.33 and 2.82 (d, AB, 4H, *J* = 7.5, 10), 1.68 (s, 6H), 0.96 (s, 9H), 0.16 (s, 6H). – ^{13}C NMR: δ = 159.9, 156.8, 153.4, 146.8, 134.7, 134.1, 129.2, 125.2, 119.5, 115.0, 111.8, 104.7, 36.5, 36.3, 25.4, 25.3, 17.8, –4.8. – MS; *m/z* (%): 412 (19) [M$^+$], 297 (21), 221 (100), 163 (10), 73 (20). – HRMS ($C_{24}H_{32}O_4Si$): calcd. 412.2070; found 412.2051. – $C_{24}H_{32}O_4Si$ (412.6): calcd. C 69.87, H 7.82; found C 69.80, H 7.73.

5-[2-(4-Hydroxyphenyl)ethyl]-2,2-dimethylbenzo[1,3]dioxin-4-one (**35**): To a solution of compound **34** (85 mg, 0.21 mmol) in EtOAc (3 ml), TBAF (70% in water, 0.5 ml) was added and the mixture stirred for 10 min. Extractive work-up followed by flash chromatography with hexane/ethyl acetate (4:1→1:1) gave **35** as colorless crystals (59 mg, 96%); m.p. 151–152 °C. – IR: ν̃ = 3328 cm^{-1}, 3031, 2996, 2931, 2862, 1711, 1607, 1581, 1519, 1478, 1444, 1388, 1317, 1301, 1263, 1227, 1210, 1165, 1079, 1053, 1029, 926,

826, 812, 702, 669, 643, 587. – ^{1}H NMR: δ = 7.37 (t, 1H, *J* = 8), 7.08 and 6.76 (AB, 4H, *J* = 8.5), 6.86 (dd, 1H, *J* = 1.5, 8), 6.80 (dd, 1H, *J* = 1.5, 8), 3.32 and 2.82 (dAB, 4H, *J* = 7.5, 10), 1.68 (s, 6H). – ^{13}C NMR: δ = 160.1, 157.2, 154.0, 147.3, 135.3, 133.7, 129.7, 125.5, 115.5, 115.2, 112.1, 105.2, 36.9, 36.7, 25.6. – MS; *m/z* (%): 298 (24) [M^+], 240 (68), 134 (100), 107 (93), 105 (15), 77 (20). – HRMS ($C_{18}H_{18}O_4$): calcd. 298.1205; found 298.1189. – $C_{18}H_{18}O_4$ (298.3): calcd. C 72.47, H 6.08; found C 72.22, H 5.97.

Lunularic Acid (**36**): A solution of compound **35** (114 mg, 0.382 mmol) in DMSO (5 ml) and aq. KOH (48%, 0.5 ml) was stirred at 80°C for 3 h. For work-up the mixture was diluted with EtOAc, acidified with HCl (pH ≈ 1) and the EtOAc phase repeatedly washed with water. The organic layer was dried (Na_2SO_4) and concentrated and the crude residue chromatographed (hexane/EtOAc/HOAc, 60:35:5) affording **36** (89 mg, 90%) as colorless crystals; m.p. 193–195°C (ref.[17g] 201–202°C, ref.[17h] 194–195°C). – IR: $\tilde{\nu}$ = 3465–2583 cm^{-1}, 1652, 1605, 1514, 1466, 1443, 1322, 1292, 1245, 1207, 1169, 1024, 1009, 998, 901, 825, 772, 765, 703, 643, 593, 523. – ^{1}H NMR ([D_6]DMSO): δ = 7.11 (t, 1H, *J* = 8), 6.98 (d, 2H, *J* = 8.3), 6.60–6.69 (m, 4H), 2.88 and 2.68 (dAB, 4H, *J* = 6.1, 11.2). – ^{13}C NMR ([D_6]DMSO): δ = 170.9, 157.3, 154.9, 141.5, 131.8, 130.5, 128.8, 120.0, 119.3, 114.7, 113.7, 36.4, 36.3. – MS; *m/z* (%): 258 (12) [M^+], 107 (100).

[1] For a review see: P. Potier, *Chem. Soc. Rev.* **1992**, *92*, 113–119.

[2] [2a] Review: K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 38–69; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15. – [2b] For a recent highlight locating the taxol binding site on tubulin see: E. Nogales, S. G. Wolf, I. A. Khan, R. F. Luduena, K. H. Downing, *Nature* **1995**, *375*, 424–427.

[3] Combretastatin A-4 and A-5: [3a] G. R. Pettit, S. B. Singh, E. Hamel, C. M. Lin, D. S. Alberts, D. Garcia-Kendall, *Experientia* **1989**, *45*, 209–211. – [3b] G. R. Pettit, S. B. Singh, M. R. Boyd, E. Hamel, R. K. Pettit, J. M. Schmidt, F. Hogan, *J. Med. Chem.* **1995**, *38*, 1666–1672. – [3c] C. M. Lin, H. H. Ho, G. R. Pettit, E. Hamel, *Biochemistry* **1989**, *28*, 6984–6991. – [3d] J. A. Woods, J. A. Hadfield, G. R. Pettit, B. W. Fox, A. T. McGown, *Brit. J. Cancer* **1995**, *71*, 705–711.

[4] Other members of the combretastatin series: [4a] G. R. Pettit, S. B. Singh, *Can. J. Chem.* **1987**, *65*, 2390–2396. – [4b] G. R. Pettit, S. B. Singh, M. L. Niven, E. Hamel, J. M. Schmidt, *J. Nat. Prod.* **1987**, *50*, 119–131.

[5] Review: D. L. Sackett, *Pharmac. Ther.* **1993**, *59*, 163–228.

[6] [6a] G. R. Pettit, C. Temple, V. L. Narayanan, R. Varma, M. J. Simpson, M. R. Boyd, G. A. Rener, N. Bansal, *Anti-Cancer Drug Design* **1995**, *10*, 299–309. – [6b] R. T. Brown, B. W. Fox, J. A. Hadfield, A. T. McGown, S. P. Mayalarp, G. R. Pettit, J. A. Woods, *J. Chem. Soc., Perkin Trans. 1* **1995**, 577–581. – [6c] S. B. Bedford, C. P. Quarterman, D. L. Rathbone, J. A. Slack, R. J. Griffin, M. F. G. Stevens, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 157–160. – [6d] A. Ramacciotti, R. Fiaschi, E. Napolitano, *Tetrahedron: Asymmetry* **1996**, *7*, 1101–1104.

[7] For leading references on combretastatin analogues see i.a.: [7a] Z. Getahun, L. Jurd, P. S. Chu, C. M. Lin, E. Hamel, *J. Med. Chem.* **1992**, *35*, 1058–1067. – [7b] M. Cushman, D. Nagarathnam, D. Gopal, H. M. He, C. M. Lin, E. Hamel, *J. Med. Chem.* **1992**, *35*, 2293–2306. – [7c] C. J. Andres, J. E. Bernardo, Q. Yan, S. B. Hastie, T. L. Macdonald, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 565–570. – [7d] R. Shirai, K. Tokuda, Y. Koiso, S. Iwasaki, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 699–704. – [7e] M. Medarde, R. Pelaez-Lamamie de Clairac, A. C. Ramos, E. Caballero, J. L. Lopez, D. G. Gravalos, A. San Feliciano, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 229–232. – [7f] J. D. Olszewski, M. Marshalla, M. Sabat, R. J. Sundberg, *J. Org. Chem.* **1994**, *59*, 4285–4296.

[8] Reviews: [8a] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483. – [8b] A. Suzuki, *Pure Appl. Chem.* **1994**, *66*, 213–222. – [8c] A. Suzuki, *Pure Appl. Chem.* **1991**, *63*, 419–422. – [8d] A. Suzuki, *Pure Appl. Chem.* **1985**, *57*, 1749–1758.

[9] [9a] A. Fürstner, G. Seidel, *Tetrahedron* **1995**, *51*, 11165–11176. – [9b] See also: J. A. Soderquist, K. Matos, A. Rane, J. Ramos, *Tetrahedron Lett.* **1995**, *36*, 2401–2402.

[10] There is some precedence for the use of $B(OMe)_3$ as mediator for in situ Suzuki-type reactions of aryllithium compounds, c.f.: [10a] W. A. Cristofoli, B. A. Keay, *Tetrahedron Lett.* **1991**, *32*, 5881–5884. – [10b] S. P. Maddaford, B. A. Keay, *J. Org. Chem.* **1994**, *59*, 6501–6503. – [10c] T. Gillmann, T. Hülsen, W. Massa, S. Wocadlo, *Synlett* **1995**, 1257–1259.

[11] The ^{11}B-NMR spectrum of [HC≡CNa · $B(OMe)_3$] prepared in situ shows peaks at δ = +18.06, +2.63, +0.83, and −4.31 relative to $BF_3 \cdot Et_2O$ as external standard.

[12] For leading references see: [12a] A. E. Stiegman, E. Graham, K. J. Perry, L. R. Khundkar, L.-T. Cheng, J. W. Perry, *J. Am. Chem. Soc.* **1991**, *113*, 7658–7666. – [12b] T. Hiyama, N. Wakasa, T. Ueda, T. Kusumoto, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 640–642. – [12c] A. Scrivanti, U. Matteoli, *Tetrahedron Lett.* **1995**, *36*, 9015–9018. – [12d] E. Yashima, S. Huang, T. Matsushima, Y. Okamoto, *Macromolecules* **1995**, *28*, 4184–4193, and references cited therein.

[13] For the use of trialkylethynylstannanes see: J. K. Stille, J. H. Simpson, *J. Am. Chem. Soc.* **1987**, *109*, 2138–2152.

[14] For leading references on the use of ethynyltrimethylsilane see: [14a] S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627–630. – [14b] W. B. Austin, N. Bilow, W. J. Kelleghan, K. S. Y. Lau, *J. Org. Chem.* **1981**, *46*, 2280–2286. – [14c] L. Brandsma, H. G. M. van den Heuvel, H. D. Verkruijsse, *Synth. Commun.* **1990**, *20*, 1889–1892. – [14d] T. Sakamoto, M. Shiraiwa, Y. Kondo, H. Yamanaka, *Synthesis* **1983**, 312–314. – [14e] For the use of 2-methyl-3-butyn-2-ol as acetylene equivalent see: S. J. Havens, P. M. Hergenrother, *J. Org. Chem.* **1985**, *50*, 1763–1765.

[15] Coupling of haloarenes with acetylene gas under Sonogashira conditions (Et_2NH, CuI, Pd^0 cat.) does not afford the corresponding ethynylarene but leads to the internal 1,2-diarylalkyne, see: [15a] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467–4470. – [15b] M. Pal, N. G. Kundu, *J. Chem. Soc., Perkin Trans. 1* **1996**, 449–451.

[16] For the use of ethynylzinc halides see: A. O. King, E. I. Negishi, F. J. Villani, A. Silveira, *J. Org. Chem.* **1978**, *43*, 358–360.

[17] Isolation and properties: [17a] I. F. M. Valio, R. S. Burdon, W. W. Schwabe, *Nature* **1969**, *223*, 1176–1178. – [17b] J. Gorham, *Phytochemistry* **1977**, *16*, 249–253. – [17c] J. Gorham, *Phytochemistry* **1978**, *17*, 99–105. – [17d] S. Abe, Y. Ohta, *Phytochemistry* **1983**, *22*, 1917–1920. – [17e] R. J. Pryce, *Phytochemistry* **1972**, *11*, 1355–1364. – Syntheses: [17f] Y. Arai, T. Kamikawa, T. Kubota, *Tetrahedron Lett.* **1972**, 1615–1617. – [17g] T. Eicher, K. Tiefensee, R. Pick, *Synthesis* **1988**, 525–529. – [17h] D. B. Reitz, S. M. Massey, *J. Org. Chem.* **1990**, *55*, 1375–1379. – [17i] Y. Arai, T. Kamikawa, T. Kubota, Y. Masuda, R. Yamamoto, *Phytochemistry* **1973**, *12*, 2279–2282. – [17j] S. Huneck, K. Schreiber, *Phytochemistry* **1977**, *16*, 1013–1016.

[18] [18a] A. Hadfield, H. Schweitzer, M. P. Trova, K. Green, *Synth. Commun.* **1994**, *24*, 1025–1028. – [18b] See also: R. G. Dushin, S. J. Danishefsky, *J. Am. Chem. Soc.* **1992**, *114*, 655–659. – [18c] For the use of this triflate in the synthesis of a fungal metabolite with GABA-receptor inhibiting properties see: A. Fürstner, I. Konetzki, *Tetrahedron*, submitted.

[19] [19a] 9-MeO-9-BBN: H. C. Brown, E. F. Knights, C. G. Scouten, *J. Am. Chem. Soc.* **1974**, *96*, 7765–7770. A 1 M solution in hexane can be purchased from Aldrich Chem. Co. – [19b] 9-BBN dimer: P. Binger, R. Köster, *Inorg. Synth.* **1974**, *15*, 147–149.

[20] T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158–163.

[21] [21a] M. Kato, F. Kido, M. D. Wu, A. Yoshikoshi, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1516–1521. – [21b] D. A. Dawson, W. F. Reynolds, *Can. J. Chem.* **1975**, *53*, 373–382. – [21c] A. I. Meyers, L. Snyder, *J. Org. Chem.* **1993**, *58*, 36–42. – [21d] S. Kano, T. Yakomatsu, S. Shibuya, *J. Org. Chem.* **1978**, *43*, 4366–4367.

[96204]