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Synthesis Of Phenolic Natural Products Using Palladium Catalyzed Coupling Reactions

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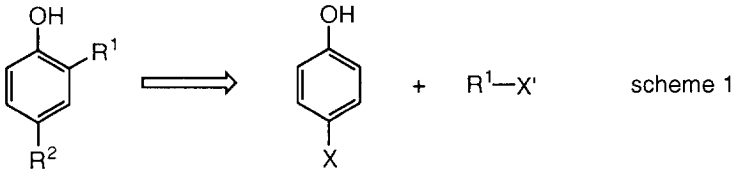
Derivatives of 2,4-diiodophenol are shown to undergo palladium catalyzed carbonylation and alkyne coupling reactions in excellent to moderate yield and high regioselectivity. The scope of these reactions is explored. Palladium catalyzed reactions are employed as the key steps in the synthesis of three phenolic natural products: Plicatin B, Drupanin and Eutypine.

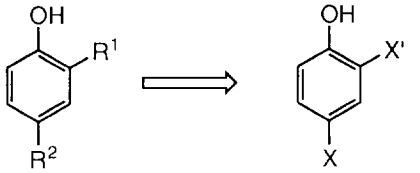
ortho,para-Disubstituted phenols are common amongst natural products. A reasonable synthetic strategy is the sequential addition of the two substituents to the phenol. *ortho*-Substituents which can be derived from reactive alkyl halides, such as the common prenyl group,[1] can be easily incorporated by alkylation of the sodium phenoxide in a non-polar solvent.[2] An attractive strategy for attaching the *para* substituent is the use of palladium catalyzed coupling procedures (scheme 1).[3] As these generally involve mild conditions without strong acids and bases, pre-existing functionality is excellently tolerated.



scheme 1

X,X' = halide, leaving group

For phenolic compounds where the *ortho* substituent cannot be attached by simple alkylation, it would be desirable to use palladium catalyzed coupling reactions in both cases (scheme 2). For selectivity to be achieved, this would require the use of two different halogens at the *ortho* and *para* positions. The selective reactions of iodides, bromides, triflates and acid chlorides have been amply demonstrated.[4]

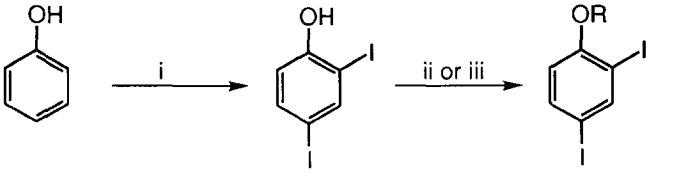


scheme 2

An alternative strategy would be to use the same halogen, preferably the more reactive iodine (X=X'=I), in both *ortho* and *para* positions. Successful and selective coupling of two different substituents would require

regioselective reactions. This has been demonstrated in a handful of examples involving alkenes, pyridines, pyrimidines, imidazoles and purines.[5]

We turned our attention to the problem of regioselective coupling.[6] We selected the acetate (**1a**) and t-BOC (**1b**) derivatives of 2,4-diiodophenol (**2**). These were easily prepared by iodination of phenol[7] and acylation with acetyl chloride or di-t-buyl dicarbonate (scheme 3).[8] We chose to examine four representative palladium catalyzed reactions: Castro-Stephens (Sonogashira) coupling of alkynes,[9] Stille coupling of stannanes,[10] formylation[11] and Heck arylation of alkenes.[12]



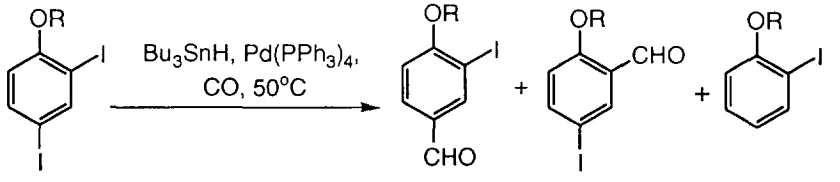
scheme 3

(**2**)

(**1a**) R = Ac
(**1b**) R = t-BOC

i. KI, I_2, KOH or NaI, NaOH, NaOCl; ii. AcCl, Et_3N, DMAP,
iii. $(t\text{-BuOCO})_2O$, K_2CO_3, 18-Crown-6

Formylation of (**1a**) was carried out using the method of Stille[11]: slow addition of a solution of tributyltin hydride in toluene (syringe pump over 24 hours) under one atmosphere of carbon monoxide using a catalytic amount of tetrakis(triphenylphosphine)palladium (0) at 50°C. The major product was the aldehyde (**3a**) as a *ca* 10:1 mixture with its regioisomer (**4**) in a combined yield of 40% (scheme 4). The regiochemistry was determined by nOe experiments: in particular, irradiation of the aldehydic proton caused enhancement (*ca* 15%) of two aryl protons, which is consistent only with the structure (**3a**). The structure was also confirmed by comparison to authentic material. A minor by-product observed in some runs was the *para*-reduced compound (**5**), caused by reduction of the intermediate palladium complex without CO insertion. This was generally observed when Bu_3SnH addition was too fast. The t-BOC protected phenol (**1b**) also reacted selectively to give aldehyde (**3b**). In this case, none of the other isomer was detected.



scheme 4

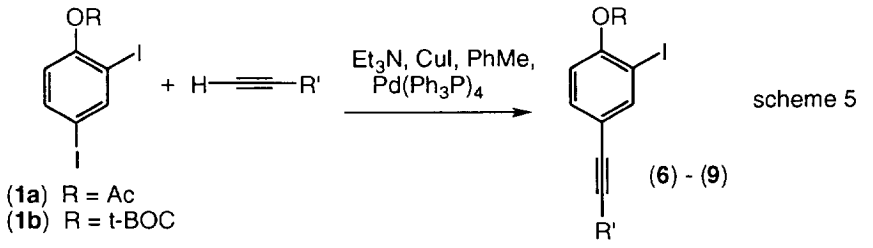
(**1a**) R = Ac
(**1b**) R = t-BOC

(**3a**) 40%
(**3b**) 49%

(**4**) R = Ac

(**5**)

Coupling of either diiodide (**1a**) or (**1b**) with terminal alkynes in the presence of triethylamine and catalytic amounts of tetrakis(triphenylphosphine)palladium (5 mole%) and copper (I) iodide (20 mole%) at room temperature, overnight, yielded single regioisomers (**6**), (**7**), (**8**) and (**9**) (table 1, scheme 5).

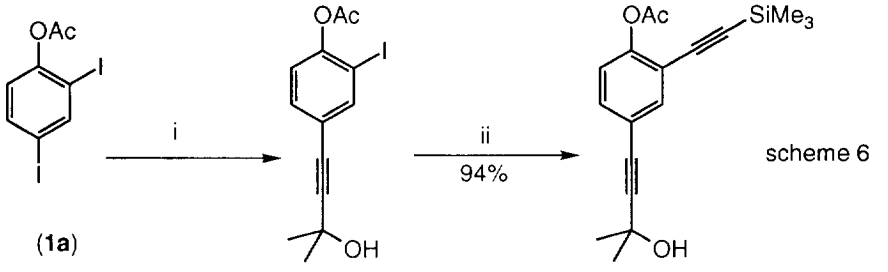


scheme 5

Table 1 Coupling of Diiodides with Terminal Alkynes

diiodide	R'	product	yield (%)
1a	n-Bu	**6a**	95
1b	n-Bu	**6b**	70
1a	Me_3Si	**7a**	80
1b	Me_3Si	**7b**	71[13]
1a	$BnOCH_2$	**8a**	69
1b	$BnOCH_2$	**8b**	73
1a	$Me_2C(OH)$	**9a**	78

Further coupling of the products was possible to give specific isomerically pure aryl diynes such as (**10**) (scheme 6). The reaction conditions for the second coupling were the same as those for the first, indicating that the relative reactivities of the two iodines are quite close, but sufficiently distinct to give selectivity.



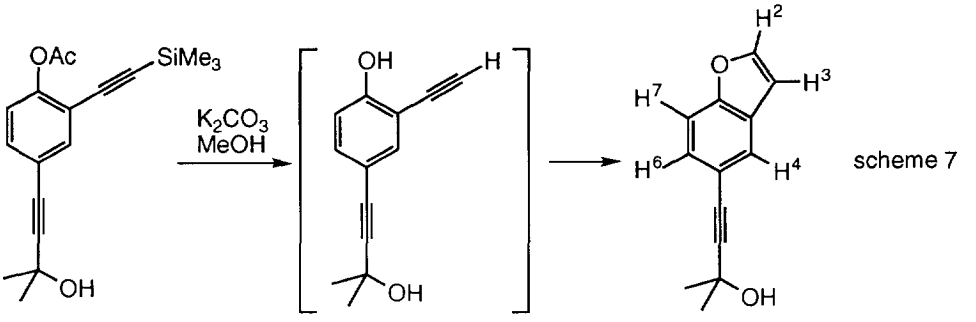
scheme 6

i.$HC{\equiv}C(CH_3)_2OH$, $(Ph_3P)_4Pd$, CuI, Et_3N; ii. $HC{\equiv}CSiMe_3$, $(Ph_3P)_4Pd$, CuI, Et_3N

This double coupling sequence also served to prove the regioselectivity of the reaction (scheme 7). After removal of the acetyl and trimethylsilyl groups of diyne (**10**) with potassium carbonate in methanol, the resulting alkynyl phenol (**11**) underwent cyclization *in situ* to give the benzofuran (**12**) in 58% yield.[14]

In the ^1H NMR spectrum, all of the protons were resolved at 200 MHz. H2 (benzofuran numbering) appeared as a doublet at 7.62 ppm, coupling to H3 (J = 2.2 Hz). H3 appeared as a double doublet at 6.72 ppm, coupling with H2 (J=2.2 Hz) and with H7 (J=0.8 Hz). This latter coupling is characteristic of benzofurans.[15]

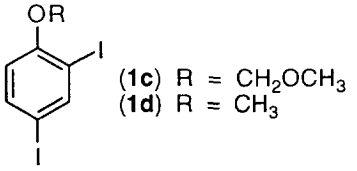
The corresponding values for benzofuran itself are in good agreement: H2: 7.52 ppm, d, J =2.5 Hz; H3: 6.66 ppm, dd, J = 2.5, 0.9 Hz.[16] The other aryl protons showed the expected coupling. All of the NMR coupling relationships were confirmed by a COSY experiment.



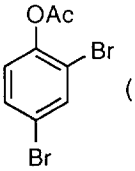
scheme 7

(10) **(11)** **(12)**

Ether protecting groups were found to be unsuitable. Under the same conditions the MOM and methyl ethers (**1c**) and (**1d**), gave mixtures of products. The acetate (**13**) of commercially available 2,4-dibromophenol was also unsuitable for the alkyne coupling reaction. In this case, two inseparable isomers were produced in a ratio of *ca* 5:1, determined by ^{1}H NMR.



(**1c**) R = CH_2OCH_3
(**1d**) R = CH_3

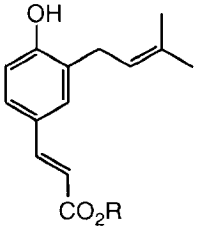


(**13**)

Attempted Stille coupling of diiodide (**1a**) with phenyltrimethyltin, even using Cu(I) catalysis,[17] was unsuccessful. Arylation of methyl acrylate with diiodide (**1a**) under Heck conditions also failed. This may be attributed to drastic slowing of transmetallation and alkene insertion respectively by the electron rich ring[18]. As other palladium catalyzed reactions work for this molecule under mild conditions, failure of oxidative addition cannot be the cause. The Heck reaction using an electron-rich alkene, n-butyl vinyl ether, proceeded under the same conditions, but give a complex mixture of products.

Synthesis Of Plicatin B

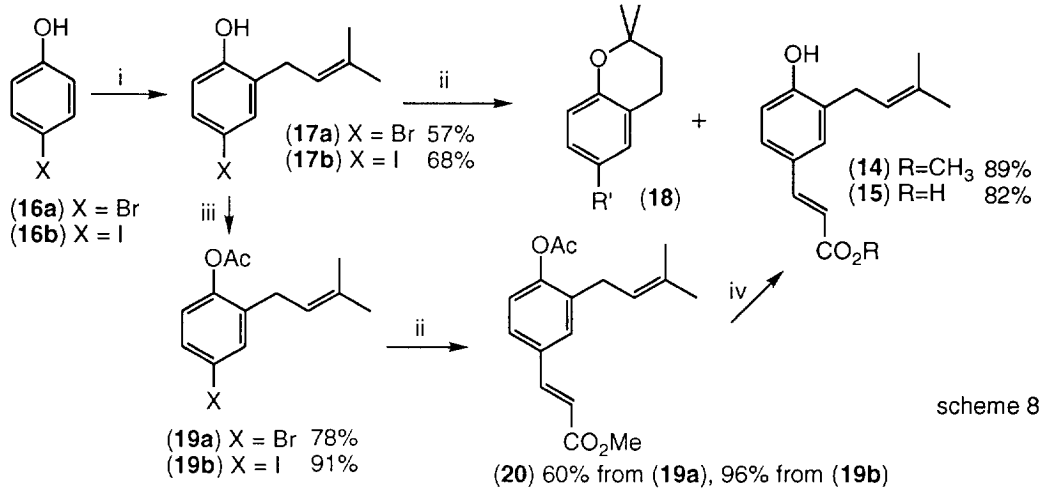
Plicatin B (**14**) is an anti-microbial compound, isolated from *psoralea juncea* and other species.[19] The corresponding carboxylic acid, drupanin (**15**) , has also been isolated.[20]



(**14**) R = CH_3
(**15**) R = H

The *ortho*-prenyl group makes these molecules a target from the first strategy, alkylation-coupling (scheme 1, 8).[21] *para*-Bromophenol (**16a**) and *para*-iodophenol (**16b**) were C-prenylated *via* their sodium salts.[2] Heck reaction of the prenylated bromophenol (**17a**) with methyl acrylate gave no detectable alkene product. The prenylated iodophenol (**17b**) did react to give a low yield of Plicatin B (33%) as well as recovered starting material and other products which appeared to be dimethylchromans (**18**, R' = I, $CH{=}CHCO_2Me$) resulting from acid catalyzed attack of the phenolic oxygen on the double bond. Bromophenols are known to be only moderately reactive at best in the Heck reaction.[22] The additional alkyl group makes the ring more electron rich, slowing alkene insertion further. The phenolic hydroxyl must be converted to a less electron donating group to allow the Heck reaction to work efficiently.[21,23]

The corresponding acetates, (**19a**) and (**19b**), reacted with methyl acrylate under Heck conditions to give Plicatin B acetate (**20**) in 60% or 96% yields under optimum conditions (5 mole% $Pd(OAc)_2$, 10 mole% tri-*o*-tolylphosphine, triethylamine, toluene, 100°C, 24 hours). Omission of the added phosphine resulted in lower yields and precipitation of palladium metal before the starting material was consumed.

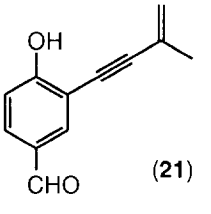


scheme 8

i. NaH, toluene, then $Me_2C{=}CHCH_2Br$; ii.$H_2C{=}CHCO_2Me$, $Pd(OAc)_2$, $(o\text{-tol})_3P$, Et_3N;
iii. AcCl, Et_3N, DMAP; iv. MeOH, K_2CO_3 or NaOH, THF, H_2O

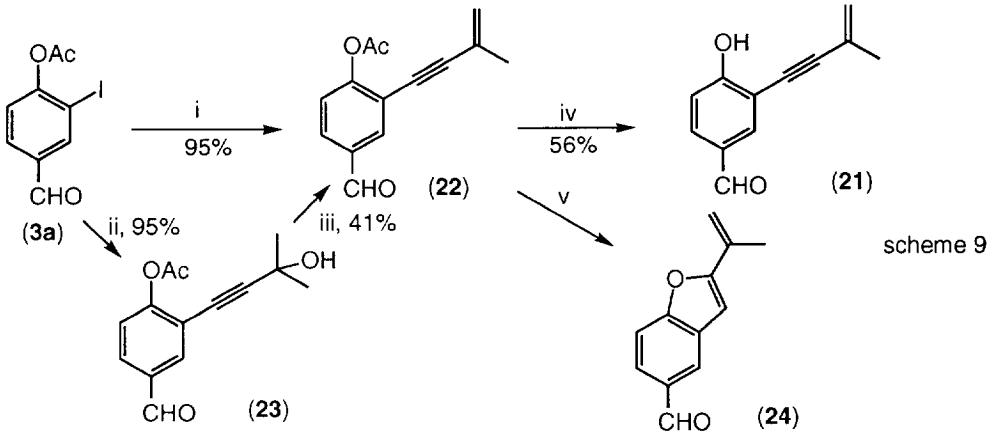
The acetate was removed by methanolysis in the presence of potassium carbonate to give Plicatin B (**14**) Saponification of (**20**) with sodium hydroxide yielded Drupanin (**15**). Both samples were spectroscopically identical to the natural products.

Synthesis of Eutypine



(**21**)

Eutypine (**21**) is the most active of a group of phytoxins isolated from the fungus *Eutypa lata* which is responsible for vine dieback in parts of Europe. Several synthetic routes have been described by Tabacchi.[24] The aldehyde (**3a**) obtained by formylation of diiodide (**1a**) is an appropriate precursor for Eutypine, following the dicoupling strategy (scheme 2). Coupling of aldehyde (**1a**) with 3-methyl-3-buten-2-yne gave an excellent yield of the product (**22**). The reaction was somewhat capricous, presumably due to the sensitivity of eneyne. An alternative procedure was found to be more reliable, but lower yielding: coupling with 2-methyl-3-butyn-1-ol to give alcohol (**23**), followed by dehydration. With the acetate (**22**) in hand, only saponification was necessary. Under various mild conditions (NaOH, NH_3 (aq), MeOH/Et_3N), the only isolable product was the benzofuran (**24**) which arises by cyclization of the phenoxide of eutypine.[25] Ultimately, we found that saponification with lithium hydroxide in aqueous THF proceeded smoothly in 56% yield giving eutypine (**21**) with no detectable benzofuran formation.[26]



scheme 9

i. $HC{\equiv}CC(CH_3){=}CH_2$, $(Ph_3P)_4Pd$, CuI, Et_3N; ii. $HC{\equiv}CC(CH_3)_2OH$, $(Ph_3P)_4Pd$, CuI, Et_3N;
iii. $SOCl_2$, C_5H_5N; iv. LiOH, H_2O, THF; v. MeOH, K_2CO_3, or NH_3 (aq) or MeOH, Et_3N or NaOH (aq).

Palladium catalyzed reactions clearly allow the systematic construction of complex phenolic molecules. Further applications to the synthesis of phenolic and benzofuran natural products are in progress.

Acknowledgments: We thank the Robert A. Welch Foundation and the University of North Texas for financial support of this work.

EXPERIMENTAL

General. All melting points are uncorrected. NMR spectra were obtained on Varian Gemini-200 NMR spectrometer in $CDCl_3$ at 200 MHz (^1H) or 50 MHz (^{13}C). Chemical shifts (δ) are in ppm and coupling constants (J) are in Hz. Infrared spectra were obtained on MIDAC FTIR spectrometer, neat or as nujol mulls. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All reactions were followed by TLC: glass or plastic sheets coated with silica gel 60 F_{254} (Merck). Flash chromatography was carried out on

silica gel: 60 Å, 230-400 Mesh. Dichloromethane was distilled from calcium hydride, tetrahydrofuran was distilled from sodium/ benzophenone and toluene was distilled from sodium. Triethylamine and N-ethyldiisopropylamine were distilled from potassium hydroxide and stored over activated molecular sieves (3Å). Tetrakis-(triphenylphosphine)palladium(0) and bis(triphenylphosphine)palladium(II) chloride were prepared according to published procedures.[3] The organic layers were dried with magnesium sulfate. Evaporation refers to rotary evaporation of solvent under aspirator pressure.

2,4-Diiodophenyl acetate (1a): Acetyl chloride (22 µl, 3.1 mmole) was added dropwise to a solution of triethylamine (435 µl, 3.1 mmole), crude 2,4-diiodophenol (**2**) (900 mg, 2.6 mmole) and DMAP (5 mole%) in dichloromethane (20 ml) at 0°C. The nixture was stirred for one hour, then washed with aqueous ammonium chloride and aqueous sodium bicarbonate. The organic layer was dried and evaporated. The residue was purified by flash chromatography (4% ether/hexane) to give the acetate (**1a**) as a white solid. m.p. 69-71°C [litt 70-71°C[7]], ^{1}H NMR 8.15 (1H, d, J=2, H3), 7.66 (1H, dd, J=8.5, 2, H5), 6.85 (1H, J=8.5, H6), 2.36 (3H, s, Me); ^{13}C NMR 168.2, 151.2, 146.9, 138.4, 124.6, 92.0, 90.7, 21.1; ir/cm^{-1}: 2955, 2932, 1753, 1562, 1186.

t-Butyl 2,4-diiodophenyl carbonate (1b): Di-t-butyl dicarbonate (1.1 ml, 4.8 mmole) was added to a suspension of anhydrous potassium carbonate (899 mg, 6.5 mmole) in THF (15 ml) containing 2,4-diiodophenol (**2**) (1.5 g, 4.3 mmole) and a catalytic amount of 18-Crown-6 under nitrogen at 0°C. The mixture was stirred overnight, then taken up in ether and washed with saturated aqueous sodium chloride. The organic layer was dried and evaporated. The residue was purified by flash chromatography (2% ether/hexane) to give the carbonate (**1b**) as an oil (1.1 g, 59%). ^{1}H NMR d 8.14 (1H, d, J=1.9, H3), 7.66 (1H, dd, J=8.3, J=1.9, H5), 6.92 (1H, d, J=8.3, H6), 1.58 (9H, s, t-Bu); ^{13}C NMR 151.94 (C=O), 151.0 (C̲Ot-BOC), 147.46, 139.0, 124.9, 92.58 (C-I), 91.19 (C-I), 85.04 (OC̲Me$_3$), 28.18 (Me); ir/cm^{-1} 2585.9, 2933.9, 1761.1 (C=O), 1566.2, 1462.1, 1375.3, 1259.5, 1143.8, 1039.6, 889.24; m/z 346 (M$^+$-tBOC), 219 (M$^+$-tBOC-I), 127 (I$^+$); analysis calc. for $C_{11}H_{12}O_3I_2$: C 29.62, H 2.71, found: C 29.80, H 2.56.

Formylation of 2,4-diiodophenol derivatives

The glassware was soaked in 1M potassium hydroxide solution for one hour. A solution of tributyltin hydride (1.1-1.5 equivalent) in toluene (3 ml) was added dropwise over twenty four hours to a mixture of the diiodide, (**1a**) or (**1b**), (100mg, 1.0 equivalent) and tetrakis(triphenylphosphine)palladium (0) (5 mole%) in toluene (2 ml). The mixture was stirred under carbon monoxide (1 atm) at 50°C. Saturated aqueous potassium fluoride (4 ml) was added and the mixture was stirred for one hour, filtered through celite, then taken up in ether. The organic layer was dried and evaporated. The residue was purified by flash chromatography eluting with ether/hexane to give the aldehyde.

4-Acetoxy-3-iodobenzaldehyde (3a). White needles, m.p. 48-49°C; ^{1}H NMR 9.88 (1H, s, CHO), 8.30 (1H, d, J=2.2, H3), 7.84 (1H, dd, J=8.5, J=2.2, H5), 7.24 (1H, d, J=8.5, H6), 2.37 (3H, s, Ac); ^{13}C NMR 189.89 (CHO), 168.30 (C=O), 156.22 (C̲OAc), 141.28, 135.91, 131.20, 91.86 (C-I), 21.69 (Me); ir/cm^{-1} 2915, 2857, 1757 (C=O), 1697 (C=O), 1584, 1462, 1376, 1296, 1192, 1132, 1035, 1004, 913, 828, 656; m/z 290 (M$^+$), 247 (M$^+$-Ac), 119 (M$^+$-Me-I-CHO); analysis calc. for $C_9H_7IO_3$: C 37.27, H 2.43, found: C 37.50, H2.25.

4-t-Butyloxycarbonyloxy-3-iodobenzaldehyde (3b). White solid, m.p. 79-80°C; ^{1}H NMR 9.93 (1H, s, CHO), 8.34 (1H, d, J=1.9, H3), 7.89 (1H, dd, J=8.3, J=1.9, H5), 7.35 (1H, d, J=8.3, H6), 1.59 (9H, s, t-Bu); ^{13}C NMR 189.36 (CHO), 155.71 (C=O), 149.98, 140.88, 135.33, 130.75, 123.96, 91.28, 84.95, 27.63 (C̲Me$_3$); ir/cm^{-1} 3097, 3034, 2943, 2861, 1759 (C=O), 1701 (C=O), 1588, 1461, 1375, 1283, 1256, 1223, 1193, 1150,

1135, 1007, 905, 870, 771, 683, 635; m/z 248 (M^+-tBOC), 219 (M^+-tBOC-CHO), 127 (I^+), 121 (M^+-tBOC-I); analysis calc. for $C_{12}H_{13}IO_4$: C 41.40, H 3.76, found: C 41.53, H 3.65.

Coupling reactions of 2,4-diiodophenol derivarives with terminal alkynes

Triethylamine (1-1.2 equivalent) and the terminal alkyne (1.1 equivalents for non-volatile alkynes, 1.5 equivalents for volatile alkynes) were added to a mixture of the diiodide (**1**) (1 equivalent), tetrakis-(triphenylphosphine)palladium(0) (5 mole%) and copper(I) iodide (20 mole%) in toluene under nitrogen at room temperature with exclusion of light. The mixture was stirred overnight, then taken up in ether and washed with saturated aqueous ammonium chloride (for the acetate) or sodium chloride (for the t-BOC derivative). The organic layer was dried and evaporated. The residue was purified by flash chromatography eluting with ether/hexane to give the alkyne (**6-9**) as an oil.

4-(1-Hexynyl)-2-iodophenyl acetate (6a): ^{1}H NMR 7.86 (1H, d, J=1.9, H3), 7.37 (1H, dd, J=8.3, J=1.9, H5), 7.00 (1H, d, J=8.3, H6), 2.38 (2H, m, $\equiv CCH_2$), 2.35 (3H, s, OAc), 1.53 (4H, m, CH_2CH_2), 0.95 (3H, t, J=7.1, Me); ^{13}C NMR 168.8 (C=O), 160.0 (COAc), 142.6, 133.0, 124.4, 123.0, 92.4 (C-I), 90.4 (alkyne), 78.8 (alkyne), 31.2 ($COCH_3$), 22.5, 21.7, 19.5, 14.1; ir/cm^{-1} 2963, 2938, 2872, 2232 (C≡C), 1772 (C=O), 1647, 1484, 1369, 1182, 1040, 1010, 907, 845; m/z 342 (M^+), 300 (M^+-Pr), 284 (M^+-Ac-Me), 257 (M^+-Ac-Pr), 215 (M^+-I), 172 (M^+-Ac-I), 158 (M^+-Ac-I-Me), 144 (M^+-Ac-I-Et), 129 (M^+-Ac-I-Pr), 127 (I^+); analysis calc. for $C_{14}H_{15}O_2I$: C 49.14, H 4.42, found: C 48.96, H 4.64.

2-Iodo-4-(2-trimethylsilyl-1-ethynyl)phenyl acetate (7a): ^{1}H NMR 7.94 (1H, d, J=1.9, H3), 7.44 (1H, dd, J=8.3, J=1.9, H5), 7.03 (1H, d, J=8.3, H6), 2.36 (3H, s, Ac), 0.24 (9H, s, $SiMe_3$); ^{13}C NMR 168.7 (C=O), 151.7 (COAc), 143.0, 133.4, 123.3, 123.1, 102.9 (C-I), 96.4 (alkyne), 90.5 (alkyne), 21.7 (Ac), 0.3 ($SiMe_3$); ir/cm^{-1} 2963, 2897, 2160 (C≡C), 1777 (C=O), 1477, 1368, 1258, 1182, 1040, 1005, 845, 760; m/z 358 (M^+), 343 (M^+-Me), 316 (M^+-Ac), 301 (M^+-Ac-Me), 231 (M^+-I), 188 (M^+-Ac-I), 127 (I^+), 117 (M^+-Ac-I-$SiMe_3$), 73 ($SiMe^+$); analysis calc. for $C_{13}H_{15}IO_3Si$: C 43.58, H 4.22, found: C 43.42, H 4.29.

4-(3-Benzyloxy-1-propynyl)-2-iodophenyl acetate (8a): ^{1}H NMR 7.93 (1H, d, J=1.9, H3), 7.45 (1H, dd, J=8.3, J=1.9, H5), 7.38 (5H, m, Ph), 7.06 (1H, d, J=8.3, H6), 4.67 (2H, s, CH_2), 4.39 (2H, s, CH_2), 2.37 (3H, s, Ac); ^{13}C NMR 168.9 (C=O), 151.8 (COAc), 142.9, 137.8, 133.3, 129.0, 128.6, 128.45, 123.2, 122.8 (C4), 90.7 (C-I), 87.0 (alkyne), 84.3 (alkyne), 72.3 (CH_2Ph) , 58.3 30.2 ($COCH_3$); ir/cm^{-1} 2944, 2861, 2222 (C≡C), 1765 (C=O), 1643, 1478, 1364, 1204, 1088, 1040, 1011, 910, 841, 745, 694; m/z 406 (M^+), 364 (M^+-Ac), 258 (M^+-Ac-OBn), 131 (M^+-OAc-Bn), 127 (I^+), 116 (M^+-Ac-I-CH_2OBn), 91 ($C_7H_7^+$); analysis calc. for $C_{18}H_{15}O_3I$: C 53.22, H 3.72, found C 53.47, H 3.86.

4-(3-hydroxy-3-methyl-1-butynyl)-2-iodophenyl acetate (9a): ^{1}H NMR 7.89 (1H, d, J=2.4, H3), 7.38 (1H, dd, J=8.7, J=1.6, H5), 7.02 (1H, d, J=8.5, H6), 2.36 (3H, s, Ac), 2.26 (1H, s, OH), 1.60 (6H, s, Me); ^{13}C NMR 168.8 (C=O), 151.6 (COAc), 142.7, 139.1, 123.1, 122.9, 95.6, (C-I), 90.6 (alkyne), 80.2 (alkyne), 66.0 (COH), 31.9 (Me), 21.7 ($COCH_3$); ir/cm^{-1} 3694-3100 (OH), 2986, 2934, 2228 (C≡C), 1763 (C=O), 1647, 1593, 1557, 1478, 1368, 1177, 1036, 1010, 962, 912, 847, 826; m/z 344 (M^+), 329 (M^+-Me), 302 (M^+-Ac), 287 (M^+-Ac-Me), 217 (M^+-I), 160 (M^+-Ac-I-Me), 127 (I^+); analysis calc. for $C_{13}H_{13}O_3I$: C 45.37, H 3.81, found: C 45.23, H 3.64.

t-Butyl 4-(1-hexynyl)-2-iodophenyl carbonate (6b): ^{1}H NMR 7.85 (1H, d, J=1.9, H3), 7.35 (1H, dd, J=8.3, J=1.9, H5), 7.06 (1H, d, J=8.3, H6), 2.39 (2H, t, J=6.9, $\equiv CH_2$), 1.57 (9H, s, t-Bu), 1.52 (4H, m, CH_2CH_2), 0.94 (3H, t, J=6.9, Me); ^{13}C NMR 150.6 (C=O), 147.0 (C=O), 142.1, 132.6, 123.8 (C4), 122.3, 92.0 (C-I),

90.0 (alkyne), 84.3 (alkyne), 78.3 ($O\underline{C}Me_3$), 30.6 , 27.7 ($OC(\underline{C}H_3)_3$), 22.0, 19.0, 13.6 (Me); ir/cm^{-1} 2963, 2934, 2870, 2234 (C≡C), 1765 (C=O), 1484, 1368, 1279, 1246, 1150, 1047, 889, 833; m/z 300 (M^+-tBOC), 285 (M^+-tBOC-Me), 257 (M^+-tBOC-Pr), 158 (M^+-tBOC-I-Me), 144 (M^+-tBOC-I-Et), 130 (M^+-tBOC-I-Pr), 127 (I^+), 115 (M^+-tBOC-I-Bu), 101 ($tBOC^+$), 91 (M^+-tBOC-I-hexynyl), 81 ($C_6H_9^+$), 57 (Bu^+), 43 (Pr^+), 29 (Et^+), 15 (Me^+); analysis calc. for $C_{17}H_{21}O_3I$: C 51.01, H 5.29, found: C 51.06, H 5.21.

t-Butyl 2-iodo-4-(2-trimethylsilyl-1-ethynyl)phenyl carbonate (7b): ^{1}H NMR 7.93 (1H d, J=1.9, H3), 7.43 (1H, dd, J=8.3, J=1.9, H5), 7.09 (1H, d, J=8.3, H6), 1.57 (9H, s, t-Bu), 0.239 (9H, s, $SiMe_3$); ^{13}C NMR 151.9 (C=O), 151.0 ($\underline{C}OtBOC$), 143.1, 133.4, 123.3 (C4), 122.8, 102.8 (C-I), 96.4 (alkyne), 90.5 (alkyne), 84.9 ($O\underline{C}Me_3$), 28.2 (Me), 0.4 ($SiMe_3$); ir/cm^{-1} 2972, 2907, 2164 (C≡C), 1771 (C=O), 1489, 1376, 1259, 1161, 1047, 951, 845, 760; m/z 316 (M^+-tBOC), 301 (M^+-tBOC-Me), 174 (M^+-tBOC-Me-I), 127 (I^+), 115 (M^+-tBOC-I-$SiMe_3$).

t-Butyl 4-(3-benzyloxy-1-propynyl)-2-iodophenyl carbonate (8b): ^{1}H NMR 7.92 (1H, d, J=1.9, H3), 7.44 (1H, dd, J=8.3, J=1.9, H5), 7.38 (5H, m, Ph), 7.12 (1H, d, J=8.3, H6), 4.66 (2H, s, CH_2), 4.38 (2H, s, CH_2), 1.58 (9H, s, t-Bu); ^{13}C NMR 151.9 (C=O), 151.1 ($\underline{C}Ot$-BOC), 142.9, 137.8, 133.3, 129.0, 128.6, 128.5, 123.0, 122.8, 90.7, 87.0, 85.0, 84.5, 72.3, 58.3, 28.2; ir/cm^{-1} 2986, 2928, 2855, 2226 (C≡C), 1765 (C=O), 1484, 1368, 1279, 1246, 1219, 1146, 1076, 893, 829, 748, 706; m/z 364 (M^+-tBOC), 258 (M^+-tBOC-OBn), 127 (I^+), 91 ($C_7H_7^+$); analysis calc. for $C_{21}H_{21}O_4I$: C 54.33, H 4.56, found: C 54.23, H 4.65.

4-(3-hydroxy-3-methyl-1-butynyl)-2-(trimethylsilylethynyl)phenyl acetate (10) was prepared according to the above procedure using acetate (**9**) (198 mg, 0.58 mmole), trimethylsilylacetylene (120 µl, 0.86 mmole), triethylamine (100 µl, 0.72 mmole), $(Ph_3P)_4Pd$ (33 mg, 0.03 mmole) and copper (I) iodide (11 mg, 0.06 mmole) in toluene (4 ml) to give the aryl diyne (**10**) as a viscous oil (181 mg, 94%) after flash chromatography (5, 20 and 30% ether/hexane). ^{1}H NMR 7.56 (1H, d, J=2, H3), 7.35 (1H, dd, J=8.4, J=2, H5), 7.01 (1H, d, J=8.4, H6), 2.31 (3H, s, Ac), 2.15 (1H, s, OH), 1.59 (6H, s, Me), 0.23 (9H, s $SiMe_3$); ^{13}C NMR 168.3 (C=O), 151.6 ($\underline{C}OAc$), 136.4, 132.6, 122.3, 120.8, 117.6, 100.3, 98.7, 94.4, 80.5, 65.5 (COH), 31.4, 20.7, -0.2 ($SiMe_3$); ir cm^{-1}: 3397 (OH), 2978 (CH), 2158 (C≡C), 1773 (C=O), 1487, 1370; m/z: 314 (M^+), 299 (M^+ - Me), 271 (M^+ - Ac), 257 (M^+ - CH_2CO_2), 241 (M^+ - $SiMe_3$); analysis calc. for $C_{18}H_{22}O_3Si$ C 68.75, H 7.05, found: C 68.80, H 7.00.

5-(3-hydroxy-3-methyl-1-butynyl)benzofuran (12). Potassium carbonate (80 mg, 0.58 mmole) was added to a solution of acetate (**10**) (76 mg, 0.24 mmole) in methanol (2 ml). The mixture was heated at reflux for 24 hours, then allowed to cool, diluted with ether and filtered through celite. The solvent was evaporated and the residue was purified by flash chromatography (30% ether/hexane) to give the benzofuran (**12**) as an oil (28 mg, 58%). ^{1}H NMR 7.67 (1H, dd, J=1.2, 0.8, H4), 7.62 (1H, d, J=2.2, H2), 7.43 (1H, brd, J=8.5, H7), 7.34 (1H, dd, J=8.5, 1.6, H6), 6.72 (1H, brd, J=2.2 Hz, H3), 2.18 (1H, brs, OH), 1.63 (6H, s, Me), ^{13}C NMR 154.5, 145.8, 128.0, 127.4, 117.2, 111.4, 106.4, 92.3 (alkyne), 82.4 (alkyne), 65.6, 31.5 (Me); ir/cm^{-1}: 3370 (OH), 2980, 2934, 2222 (C≡C), 1462, 1231, 1161; m/z: 200 (M^+), 185 (M^+ - Me); analysis calc. for $C_{13}H_{12}O_2$: C 77.98, H 6.04, found: C 77.74, H 5.90.

2,4-Diiodophenyl methoxymethyl ether (1c). N-Ethyldiisopropylamine (76 µl, 0.43 mmole) and chloromethyl methyl ether (33 µl, 0.43 mmole) were added to a mixture of 2,4-diiodophenol (**2**) (100 mg, 0.29 mmole) in dichloromethane (2 ml) under nitrogen at room temperature. The mixture was stirred over night, then taken up in ether and washed with water. The organic layer was dried and evaporated. The residue was

purified by flash chromatography eluting with 2% ether/hexane to give the MOM ether (**1c**) as an oil containing minor impurities (59 mg, 52%).^{1}H NMR 8.06 (1H, d, J=2.1, H3), 7.55 (1H, dd, J=8.6, J=2.1, H5), 6.83 (1H, d, J=8.6, H6), 5.21 (2H, s, CH_2), 3.49 (3H, s, Me); ^{13}C NMR 156.6 (COMOM), 147.2, 138.7, 117.1, 95.4 (CH_2), 89.02 (C-I), 85.4 (C-I), 57.0 (Me).

2,4-Diiodophenyl methyl ether (1d). A mixture of crude 2,4-diiodophenol (**2**) (1.01 g, 2.9 mmole), methyl iodide (220 µl, 3.5 mmole) and potassium carbonate (403 mg, 2.9 mmole) in acetone (5ml) was heated at reflux for 22 hours. The volatiles were evaporated and the residue was seperated between ether and water. The organic layer was dried and evaporated. The residue was purified by flash chromatography (hexane) to give the methyl ether as an oil (699 mg, 67%) containing minor impurities. ^{1}H NMR 8.02 (1H, d, J=2, H3), 7.55 (1H, dd, J=8.5, 2, H5), 6.56 (1H, d, J=8.5, H6), 3.86 (3H, s, Me); ^{13}C NMR 158.0, 146.5, 138.1, 112.7, 87.4 (CI), 83.2 (CI), 56.4; ir cm^{-1}: 3059, 3003, 2930, 2835 (CH), 1566, 1470, 1371, 1281.

4-Bromo-2-(3-methyl-2-butenyl)-phenol (17a). *p*-Bromophenol (**16a**) (245 mg, 1.4 mmole) was added to a suspension of sodium hydride (62 mg of a 60% dispersion in mineral oil, 1.6 mmole), in toluene under nitrogen. When effervescence ceased, prenyl bromide (196 µl, 1.7 mmole) was added to the resulting white suspension. The mixture was stirred overnight, then acidified with a small amount of aqueous acetic acid. The mixture was extracted with dichloromethane, dried and evaporated. The resulting yellow oil was purified by flash chromatography (5% ether/hexane) to give the phenol (193 mg, 57%) as an oil. ^{1}H NMR 7.2 (2H, m, Ar), 6,69, (1H, d, J=8 , Ar), 5.27 (1H, m, C<u>H</u>=CMe_2), 3.34 (2H, d, J=7, CH_2), 1.78 (3H, d, J=1, Me), 1.76 (3H, d, J=1, Me); ^{13}C NMR 153.2, 135.4, 132.4, 130.0, 129.3, 120.8, 117.3, 112.7, 29.3, 25.7, 17.8; ir/cm^{-1} 3414 (OH), 2976, 2924 (CH), 1601, 1584, 1489, 1414, 1265, 1107; analysis calc. for $C_{11}H_{13}OBr$: C 54.79, H 5.43, found C 54.51 H 5.66.

4-Iodo-2-(3-methyl-2-butenyl)-phenol (17b). *p*-Iodophenol (**16b**) (309 mg, 1.4 mmole) was treated with sodium hydride (62 mg, 1.5 mmole) and prenyl bromide (195 µl, 1.7 mmole) in toluene (2 ml) as described for (**17a**) and purified by flash chromatography (5% ether/hexane) to give the phenol (**17b**) as an oil (273 mg, 68%) ^{1}H NMR 7.4 (2H, m, Ar), 6.57 (1H, d, J=9, H6), 5.27 (1H, brt, J=7.3, =CH), 5.15 (1H, s, OH), 3.29 (2H, d, J=7.3, CH_2), 1.77 (6H, s, CH_3); ^{13}C NMR 154.2, 138.4, 136.2, 135.5, 129.7, 120.9, 118.0, 82.8, 29.4, 25.8, 17.9; ir/cm^{-1}: 3414, 2974, 2928, 1692, 1667, 1568, 1478, 1404, 1260, 1121, 812 cm^{-1}. Analysis calc. for $C_{11}H_{13}OI$: C, 45.85; H, 4.55; found: C, 45.75; H, 4.45.

4-Bromo-2-(3-methyl-2-butenyl)phenyl acetate (19a). Acetyl chloride (360 µl, 4.92 mmole) was added to a solution of the phenol (**17a**) (958 mg, 3.99 mmole), triethylamine (829 µl, 5.94 mmole) and a catalytic amount of DMAP in dichloromethane (10 ml) at 0°C. The mixture was stirred for two hours at room temperature, then diluted with ether and washed with ammonium chloride and sodium bicarbonate solutions. The aqueous layers were reextracted with ether. The combined organic layers were dried and evaporated. The residue was purified by flash chromatography (5% ether/hexane) to give the acetate (880 mg, 78%) as a white solid: m.p. 28-29°; ^{1}H NMR 7.36 (1H, s, Ar), 7.34 (1H, d, J=8.1, H6), 6.91 (1H, d, J=8.1, H5), 5.20 (1H, brt, J=7.4, =CH), 3.21 (2H, d, J=7.4, CH_2), 2.31 (3H, s, Ac), 1.77 (3H, m, Me), 1.70 (3H, m, Me); ^{13}C NMR 169.0 (C=O), 147.9, 135.8, 134.1, 132.8, 129.9, 120.6, 119.2, 28.5, 25.7, 20.8, 17.8; ir/cm^{-1}:2976, 2932, 2866 (CH), 1765 (C=O), 1481, 1370; analysis calc. for $C_{13}H_{15}O_2Br$: C 55.14; H 5.34, found: C 55.42, H 5.21.

4-Iodo-2-(3-methyl-2-butenyl)phenyl acetate (19b). The phenol (**17b**) (273 mg, 0.95 mmole) was treated with acetyl chloride (74 µl, 1.04 mmole), triethylamine (160 µl, 1.14 mmole) and DMAP in dichloromethane

(4 ml) as described above and purified by flash chromatography (5% ether/hexane) to give the acetate (285 mg, 91%) as a white solid. m.p. 31-32°; ^{1}H NMR 7.53 (1H, s, Ar), 7.51 (1H, d, J=8 , Ar), 6.77 (1H, d, J=8, Ar), 5.16 (1H, m, =CH), 3.18 (2H, d, J=7, CH_2), 1.75 (3H, m, Me), 1.69 (3H, m, Me); ^{13}C NMR 168.8 (C=O), 148.7, 138.7, 136.0, 135.9, 133.8, 124.2, 120.6, 90.43 (CI), 28.37, 25.61, 20.68, 17.7; ir/cm^{-1}: 2924, 2855, 1767, 1672, 1591, 1572, 1478, 1368, 1202, 1167, 1107; m/z: 330 (M^+), 288 (M^+-CH_2CO), 233 (M^+-CH_2CO-CH_2CMe_2), 161 (M^+-CH_2CO-I); analysis calc. for $C_{13}H_{15}O_2I$: C 47.29; H 4.58, found: C 47.42, H 4.78.

Plicatin acetate (20). A solution of the iodide (**19b**) (97 mg, 0.29 mmole), methyl acrylate (131 µl, 1.5 mmole), triethylamine (81 µl, 0.59 mmole), tri-*o*-tolylphosphine (9 mg, 0.03 mmole), and palladium acetate (3.3 mg, 0.015 mmole) in dry toluene (2 ml) was heated for 20 hours under nitrogen in a sealed tube. At the end of this time, a precipitate of triethylammonium iodide and some palladium metal had formed. The mixture was allowed to cool to room temperature, diluted with ether and filtered through celite. The filtrate was washed with saturated aqueous NH_4Cl. The aqueous layer was re-extracted with ether. The combined organic layers were dried and evaporated. The residue was purified by flash chromatography on silica gel (5:95 ether/ hexane) to give Plicatin B acetate (76 mg, 96%) as a white solid: m.p. 45-47°; ^{1}H NMR 7.76 (1H, d, J=16, ArCH=), 7.40 (1H, obsc. d, J=9, Ar), 7.37 (1H, s, Ar), 7.05 (1H, d, J=9, Ar), 6.38 (1H, d, J=16, $CHCO_2Me$), 5.21 (1H, app d quin, J=7.3, 1.5, =CH), 3.80 (3H, s, OMe), 3.24 (2H, brd, J=7.3, CH_2), 2.32 (3H, s, OAc), 1.76 (3H, m, Me), 1.71 (3H, m, Me); ^{13}C NMR 169.0 (C=O), 167.3 (C=O), 150.4, 144.1, 134.2, 133.8, 129.9, 126.5, 122.8, 120.9, 117.7, 51.6, 28.6, 25.7, 20.8, 17.8; m/z: 288 (M^+), 246 (M^+-CH_2CO), 191 (M^+-CH_2CO-CH_2CMe_2), 131 (M^+-CH_2CO-CH_2CMe_2-CO_2Me) ir/cm^{-1}: 3022, 2861 (CH), 1765 (C=O), 1703, 1634, 1190; analysis calc. for $C_{17}H_{20}O_4$: C 70.81; H 6.99 ; found: C 71.04; H 7.19.

Plicatin B (14). Anhydrous potassium carbonate (50 mg, 0.36 mmole) was added to a solution of Plicatin acetate (**20**) (51 mg, 0.18 mmole) in methanol (2 ml). The mixture was stirred at room temperature for three hours, acidified with ammonium chloride solution and extracted three times with dichloromethane. The combined extracts were dried and evaporated. The residue was purified by flash chromatography (10% ether/hexane) to give Plicatin B (37 mg, 89%) as a solid. m.p. 70-72°; ^{1}H NMR 7.64 (1H, d, J=16, ArCH), 7.28 (2H, m, Ar), 6.82 (1H, m, J=8.9, Ar), 6.29 (1H, d, J=16, $CHCO_2Me$), 6.16 (1H, brs, OH), 5.31 (1H, app t quin, J=7.3, 1.5, =CH), 3.80 (3H, s, OMe), 1.77 (6H, m, $=CMe_2$); ^{13}C NMR 168.2 (C=O), 156.6, 145.2, 135.0, 130.2, 127.7 (2 C's), 126.9, 121.2, 116.0, 114.6, 51.7, 29.7, 25.7, 17.8; analysis calc. for $C_{15}H_{18}O_3$: C 73.15, H 7.37, found: C 72.92, H 7.49.

Drupanin. Sodium hydroxide (10 ml of a 5% aqueous solution) was added to a solution of the acetate (880 mg, 3.06 mmole) in methanol (15 ml). The mixture was heated at reflux for one hour, cooled to 0°C and neutralized with acetic acid. The methanol was evaporated and the aqueous residue was extracted with ether. The extracts were washed with saturated ammonium chloride solution and brine, dried and evaporated. The residue was purified by flash chromatography (40% ether/hexane) to give Drupanin (579 mg, 82%) as a white solid m.p. 146-147°C. ^{1}H NMR ($CDCl_3$/d_6-DMSO) 8.7 (2H, brs, OH), 7.50 (1H, d, J=12, C<u>H</u>CO_2H), 7.16 (1H, d, J=2, H2), 7.12 (1H, dd, J=6.7, 2, H6), 6.76 (1H, d, J=6.7, H5), 6.15 (1H, d, J=12, C<u>H</u>=CH), 5.23 (m, 1H, =CH), 3.21 (2H, d, J=6.7, $ArCH_2$), 1.66 (3H, s, Me), 1.62 (3H, s, Me); ^{13}C NMR 170.1 (C=O), 157.9, 145.9, 133.4, 130.0, 129.0, 127.8, 126.3, 122.4, 115.9, 115.1, 28.9, 26.2, 18.2,

4-Acetoxy-3-(3-hydroxy-3-methyl-1-butynyl)benzaldehyde (23). Triethylamine (358 µl, 2.6 mmole) and 2-methyl-3-butyn-2-ol (251 µl, 2.6 mmole) were added to a mixture of the iodide (**3a**) (300 mg, 1.0 mmole), tetrakis(triphenylphosphine)palladium(0) (60 mg, 5 mole%) and copper(I) iodide (39 mg, 20 mole%) in toluene (6 ml) under nitrogen at room temperature with exclusion of light. The mixture was stirred overnight, then taken up in dichloromethane and washed with saturated aqueous ammonium chloride. The organic layer was dried and evaporated. The residue was purified by flash chromatography (40% ether/hexane) to give the alkyne (**23**) as a white solid (241 mg, 95%). m.p. 92-93°C. ^{1}H NMR 9.96 (1H, s, CHO), 7.99 (1H, d, J=1.9, H3), 7.87 (1H, dd, J=8.3, J=1.9, H5), 7.27 (1H, d, J=8.3, H6), 2.38 (3H, s, Ac), 2.13 (1H, brs, OH), 1.62 (6H, s, Me); ^{13}C NMR 190.2 (CHO), 168.1 (C=O), 156.0 (COAc), 134.7, 134.1, 130.3, 123.2, 118.2, 100.4, 76.0 (alkyne), 65.6 (alkyne), 31.3 (Me), 20.8 ($CO\underline{C}H_3$); ir/cm^{-1} 3408 (OH), 3067, 2926, 2864, 2731, 1767 (C=O), 1694 (C=O), 1576, 1462, 1381, 1296, 1265, 1186, 1107, 1110, 955, 903, 872, 845, 791, 730; m/z 246 (M^+), 189 (M^+-Ac-Me), 187 (M^+-CHO-2Me), 186 (M^+-AcOH), 185 (M^+-CHO-OH-Me), 157 (M^+-AcOH-CHO), 115 (M^+-Ac-CHO-C(OH)$(CH_3)_2$); analysis calc. for $C_{14}H_{14}O_4$: C 68.28, H 5.73, found: C 68.39, H 5.92.

4-Acetoxy-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (22)

a) Thionyl chloride (73 µl, 1.0 mmole) and pyridine (162 µl, 2.0 mmole) were added to a solution of the aldehyde (**23**) (123 mg, 0.5 mmole) in dichloromethane (3 ml) under nitrogen at 0°C. The mixture was stirred overnight, then taken up in dichloromethane and washed with saturated aqueous ammonium chloride and sodium bicarbonate. The organic layer was dried and evaporated. The residue was purified by flash chromatography (10% ether/hexane) to give (**22**) as an oil (47 mg, 41%) which solidified upon standing. ^{1}H NMR 9.94 (1H, s, CHO), 7.98 (1H, d, J=2.1, H3), 7.83 (1H, dd, J=8.6, J=2.3, H5), 7.26 (1H, d, J=8.4, H6), 5.42 (1H, m, C=CH), 5.36 (1H, m, C=CH), 2.35 (3H, s, Ac), 1.97 (3H, t, J=1, Me); ^{13}C NMR 190.8 (CHO), 168.6 (C=O), 156.3 (COAc), 135.2, 134.6, 131.2, 130.6, 126.7, 123.8, 123.7, 119.2 (C-I), 97.4 (alkyne), 82.5 (alkyne), 23.7 (Me), 21.3 (Me); ir/cm^{-1} 2988, 2928, 2843, 2731, 2212 (C≡C), 1777 (C=O), 1707 (C=O), 1607 (C=C), 1580, 1495, 1433, 1375, 1314, 1240, 1184, 1103, 1005, 859, 829, 820, 733; m/z 228 (M^+), 186 (M^+-Ac), 157 (M^+-Ac-CHO), 128 ($C_9H_4O^+$), 115 ($C_8H_3O^+$).

b) Triethylamine (114 µl, 0.8 mmole) and 2-methyl-1-buten-3-yne (261 µl, 2.7 mmole) were added to a mixture of (**3a**) (198 mg, 0.7 mmole), tetrakis(triphenylphosphine)palladium(0) (39 mg, 5 mole%) and copper(I) iodide (27 mg, 20 mole%) under nitrogen at room temperature with exclusion of light. The mixture was stirred overnight, then taken up in ether and washed with saturated aqueous ammonium chloride. The organic layer was dried and evaporated. The residue was purified by flash chromatography (10% ether/hexane) to give (**22**) as an oil (152 mg, 95%).

4-Hydroxy-3-(3-methylbut-3-en-1-ynyl)benzaldehyde; Eutypine; (21). Water (1.5 ml) was added to a mixture of the acetate (**22**) (31 mg, 0.14 mmole) and lithium hydroxide monohydrate (13 mg, 0.30 mmole) in THF (1.5 ml) under nitrogen at 0°C. The mixture was stirred for 30 minutes, then taken up in dichloromethane and washed with pH6 buffer. The organic layer was dried and evaporated. The residue was purified by flash chromatography (dichloromethane) to give Eutypine (**21**) as white needles (14 mg, 56%). m.p. 67-69°C; ^{1}H NMR 9.86 (1H, s, CHO), 7.90 (1H, d, J=2.4, H3), 7.80 (1H, dd, J=8.3, 2.4, H5), 7.09 (1H, d, J=8.3, H6), 6.28 (1H, brs, OH), 5.50 (1H, m, C=CH), 6.43 (1H, m, C=CH), 2.04 (3H, t, J=1, Me); ^{13}C NMR 190.7 (CHO), 161.7 (COH), 134.9, 132.3, 130.3, 126.2, 124.4, 115.9, 111.2, 99.3 (alkyne), 80.9 (alkyne), 23.8 (Me); ir/cm^{-1} 3372 (OH), 2960, 2922, 2858, 1672 (C=O), 1602 (C=C), 1564, 1498, 1458, 1379, 1327, 1271, 1140, 893, 823.

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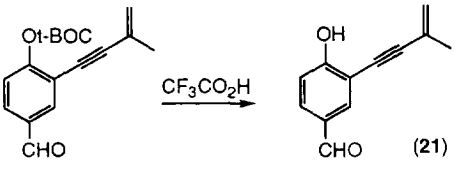
[25] This compound is apparently an artifact of the isolation of Eutypine.[24]

[26] We also examined the use of the corresponding t-BOC protected compounds, but under the acidic deprotection conditions low and erratic yields of Eutypine were obtained.



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