Total Synthesis of Siccayne

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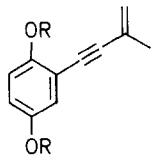
The palladium-catalyzed *C–C* coupling of 2-bromohydroquinone bis(methoxymethyl ether) with 2-methyl-3-butyn-2-ol is a key step in the six-step synthesis of the natural product siccayne [4-(2,5-dihydroxyphenyl)-2-methyl-1-buten-3-yne] from 1,4-benzoquinone.

Siccayne was first isolated from the culture broth of *Helminthosporium siccans*. Its structure was determined as 4-(2,5-dihydroxyphenyl)-2-methyl-1-buten-3-yne[1] (**1a**).



1a R = H
b R = Me
c R = Ac
d R = CH_2OMe

Later, siccayne was extracted from submerged cultures of the marine basidiomycete *Halocyphina villosa*.[2] In both cases, the antimicrobial activity of the metabolite **1a** was studied.[1,2] Recent reports[3,4] described several new aromatic compounds extracted from the culture medium of *Eutypa lata* which contained the same 3-methyl-3-buten-1-ynyl substituent as siccayne. Moreover the authors of this work[4] proposed a biogenetic pathway to epoxy-5,6,7,8-tetrahydrochroman-4-ones from siccayne; the precursor of siccayne was eutypine [4-hydroxy-3-(3-methylbut-3-en-1-ynyl)benzaldehyde].

Although siccayne has antibiotic properties no total synthesis has yet been reported. One synthetic pathway[1] stops as the dimethyl ether **1b**. Therefore, we were interested in establishing a complete pathway to siccayne; the results are presented in this work.

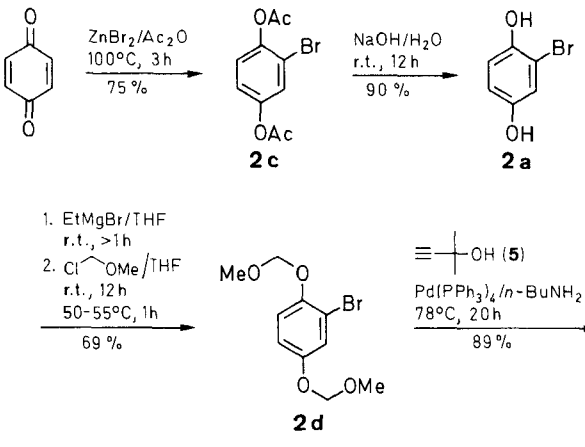
We first intented to prepare 4-(2,5-diacetoxyphenyl)-2-methyl-1-buten-3-yne (**1c**) as a precursor of siccayne, by reaction of 2-bromohydroquinone diacetate (**2c**) with 3-methyl-3-buten-1-ynylcopper(I) (**3**). In accord with analogous work,[5] the reaction did not yield the desired compound **1c** but a cyclization product thereof, the benzofuran derivative **4c**.

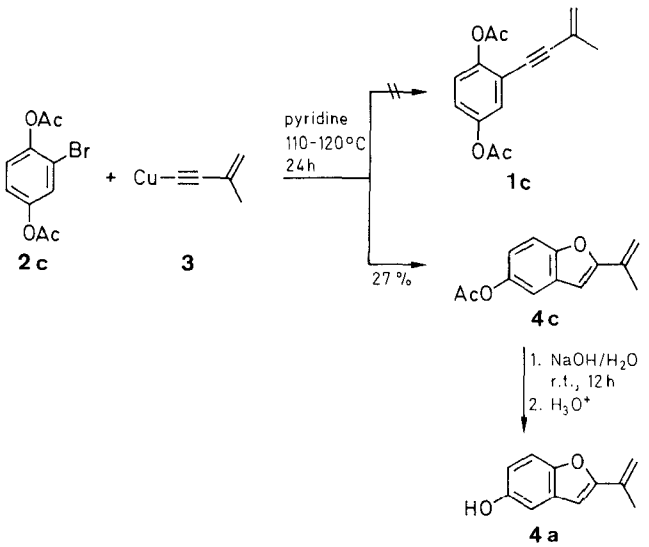
Compound **4c** was purified by column chromatography before hydrolysis to 5-hydroxy-2-isopropenylbenzofuran (**4a**).

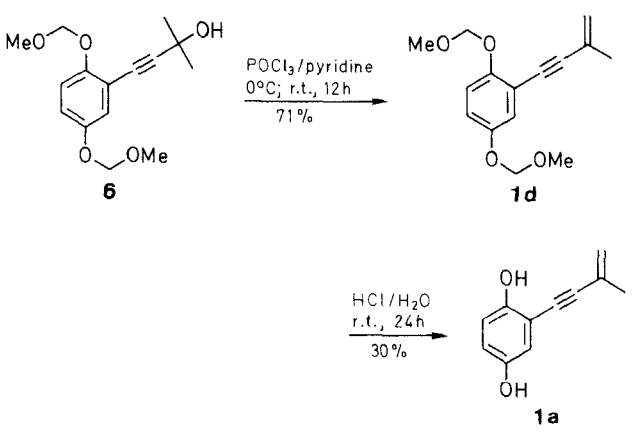
In order to prevent the cyclization reaction leading to **4c**, we replaced the diacetate **2c** by 2-bromohydroquinone dimethoxymethyl ether (**2d**). Unfortunately, the copper(I) acetylenide **3** was unreactive toward compound **2d**.

On the other hand, the aryl bromide **2d** underwent the desired coupling reaction with 2-methyl-3-butyn-2-ol (**5**) in the presence of tetrakis(triphenylphosphine)-palladium(0) in butylamine to afford the alcohol **6** as a precursor of siccayne (**1a**). The results of this reaction were similar to those reported in Lit.[6]

Because of the relative instability of siccayne (**1a**) in acidic medium it was necessary to perform the hydrolysis of the







O-methoxymethyl derivative **1d** under particularly mild conditions.

Flash chromatography was carried out according to a procedure described in Lit.[7] Purity of the compounds was verified by TLC (silica gel 60 F254) and by capillary GPC on an Intersmat IGC 121C chromatograph [WCOT fusible silica 25 m × 0.22 mm CP Wax 51; carrier gas: N_2 (0.7 bar); injection "on column" at 40 °C; temperature program 180 → 250 °C (10° min^{-1}); FID (H_2) 300 °C; compounds were in 0.1% solutions in chloroform.

1,4-Diacetoxy-2-bromobenzene (2c):[8]
1,4-Benzoquinone (28.6 g, 0.264 mol) is added to a stirred solution of $ZnBr_2$ (prepared according to Lit.[9]; 73.2 g, 0.325 mol) in Ac_2O (69 g, 0.676 mol). The mixture is heated with a boiling water bath till complete dissolution (3 h). After cooling, the solution is poured into cold H_2O (200 mL). Filtration and crystallisation ($EtOH/H_2O$, 1:1) gives compound **2c**; yield: 54 g (75%).

Bromohydroquinone (2a):
1,4-Diacetoxy-2-bromobenzene (**2c**) is hydrolyzed with 2.5 N aq NaOH (8 mol NaOH for 1 mol of **2c**). The mixture is kept at r.t. overnight, then acidified with an excess of aq HCl. Product **2a** is extracted with Et_2O; the organic layer is washed with brine, and dried (Na_2SO_4), and evaporated under normal pressure; yield: 90%; mp 109–111 °C (Lit.[10] mp 110–111 °C).

2-Bromo-1,4-bis(methoxymethoxy)benzene (2d):
Bromohydroquinone (**2a**; 3.35 g, 17.72 mmol) is carefully introduced, portionwise at r.t., into a stirred EtMgBr solution prepared from Mg (1.25 g) and EtBr (5.5 g) in THF (25 mL). A temperature rise is observed, more THF (40 mL) is added, and the mixture is maintained at r.t. for 1 h. Then chloromethoxymethane (4.1 g, 50 mmol) in THF (5 mL) is introduced at 20–25 °C, the mixture is stirred overnight at 20–25 °C, then heated for 1 h at 50–55 °C. Hydrolysis is carried out with a mixture of crushed ice (100 g), 2 M aq NH_4Cl (25 mL), and 30% aq NH_3 (5 mL). The resultant mixture is extracted with Et_2O (3 × 20 mL). The organic layer is washed with H_2O (10 mL), 2.5 N aq NaOH (2 × 20 mL), and brine (5 × 10 mL), then dried (Na_2SO_4) and evaporated. The crude product **2d** thus obtained is used in the next step without purification; yield: 3.4 g (69%).

4-[2,5-Bis(methoxymethyloxy)phenyl]-2-methyl-3-butyn-2-ol (6):
A mixture of compound **2d** (2.41 g, 8.7 mmol), 2-methyl-3-butyn-2-ol (**5**; 0.73 g, 8.7 mmol), anhydrous 1-aminobutane (20 mL), and $Pd(PPh_3)_4$ (300 mg) is heated for 20 h at 78 °C under N_2. Then, the mixture is poured into H_2O (100 mL) and extracted with Et_2O (4 × 20 mL). The organic layer is dried (Na_2SO_4) the solvent removed to give the crude product **6**; yield: 2.16 g (89%).

4-[2,5-Bis(methoxymethyloxy)phenyl]-2-methyl-1-buten-3-yne (1d):
A solution of the tertiary alcohol **6** (2.16 g, 7.7 mmol) in pyridine (5 mL) is cooled to 0 °C, and $POCl_3$ (1 g) is added. The mixture is kept at r.t. overnight and then poured onto crushed ice (100 g). The resultant mixture is extrated with Et_2O (4 × 25 mL). The organic layer is washed with brine (4 × 10 mL), dried (Na_2SO_4), and evaporated. The residual pyridine was removed by distillation with toluene (3 × 30 mL). The remaining crude product **1d** is used in the next step without purification; yield: 1.43 g (71%).

4-(2,5-Dihydroxyphenyl)-2-methyl-1-buten-3-yne (Siccayne, 1a):
Compound **1d** (1.43 g, 5.45 mmol) is hydrolyzed with 1% aqueous HCl (50 mL) at r.t. for 24 h. The resultant mixture is extracted with Et_2O (4 × 30 mL), and the extract is washed with brine (4 × 10 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The remaining siccayne is purified by column chromatography [silica gel; $CHCl_3$/EtOH (99/1)] and recrystallized from MeOH; yield: 280 mg (30%).

5-Acetoxy-2-isopropenylbenzo[*b*]furan (4c):
To a suspension of 3-methyl-3-buten-1-ynylcopper(I) (**3**, prepared according to Lit.[5]; 7.7 g, 60 mmol) in pyridine (200 mL) is added a solution of the diacetate **2c** (8.2 g, 30 mmol) in pyridine (40 mL), and the mixture is heated at reflux temperature for 24 h. Before it is

Table. Compounds **1**, **2**, **4**, and **6** Prepared

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b] or mp from Lit.	IR (KBr)[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)
1a	30	114–116 (MeOH)	115–116,[1] 114[2]	3500–3200, 2197, 1610	1.98 (dd, 3H, ^4J = 1.0, 1.4, CH_3), 5.43 (m, 2H, $=CH_2$), 6.85 (m, 3H_{arom})
1d	71	wax	$C_{15}H_{18}O_4$ (262.3)	2220, 1614, 1598, 1496	1.94 (m, 3H, CH−C$\underline{H}_3$), 3.37 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 5.04 (s, 2H, OCH_2O), 5.10 (s, 2H, OCH_2O), 5.27, 5.40 (m, 2H, $=CH_2$), 7.00 (m, 2H_{arom}), 7.15 (m, 1H_{arom})
2c	75	74–76 (EtOH/H_2O, 1:1)	71–73[8]		2.28 (s, 3H, $OCOCH_3$), 2.35 (s, 3H, $OCOCH_3$), 7.22 (m, 2H_{arom}), 7.50 (m, 1H_{arom})
2d	70	wax	$C_{10}H_{13}BrO_4$ (277.1)		3.37 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 5.13 (s, 2H, OCH_2O), 5.20 (s, 2H, OCH_2O), 7.10 (m, 2H_{arom}), 7.37 (d, 1H, ^4J = 2.5, 1H_{arom})
4c	27	76–78 (Et_2O)	$C_{13}H_{12}O_3$ (216.2)	1764, 1728, 1716, 1677, 1630, 1614, 1599, 1551, 1504	2.03 (s, 3H, C−CH_3), 2.24 (s, 3H, $OCOCH_3$), 5.14, 5.76 (2s, 2H, $=CH_2$), 6.53 (s, 1H, H-3), 6.92 (dd, 1H, ^3J = 8.8, ^4J = 2.4, H-6), 7.19 (d, 1H, ^4J = 2.4, H-4), 7.36 (d, 1H, ^3J = 8.8, H-7)
4a	98	112–114 (Et_2O)	$C_{11}H_{10}O_2$ (174.2)	3500–3300, 1693, 1673, 1626, 1618, 1610, 1595, 1551, 1500	2.12 (s, 3H, C−CH_3), 3.72 (br s, 1H, OH), 5.22 and 5.80 (2s, 2H, $=CH_2$), 6.58 (s, 1H, H-3), 6.80 (dd, 1H, ^3J = 9, ^4J = 2, H-6), 7.00 (d, 1H, ^4J = 2, H-4), 7.37 (d, 1H, ^3J = 9, H-7)
6	89	wax	$C_{15}H_{20}O_5$ (280.3)	3600–3200, 2079, 1606, 1496	1.59 (s, 6H, 2CH_3), 3.40 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 5.09 (s, 2H, OCH_2O), 5.15 (s, 2H, OCH_2O), 6.99 (s, 2H_{arom}), 7.09 (s, 1H_{arom})

[a] Melting points are uncorrected.
[b] All products gave satisfactory analyses: C ±0.3, H ±0.2.
[c] IR spectra were recorded on a Beckman Acculab 2 spectrometer.
[d] ^{1}H-NMR spectra were recorded on a Varian EM 360 spectrometer at 60 MHz.

then diluted with Et_2O (300 mL), cooled to 0 °C, and filtered. The filtrate was washed with brine (4 × 10 mL) and dried (Na_2SO_4). The solvent is evaporated and pyridine removed by distillation with toluene (3 × 50 mL). The residue is purified by flash chromatography [EtOAc/petroleum ether (bp 40 °C), 4:1]; yield: 1.75 g (27%).

5-Hydroxy-2-isopropenylbenzo[*b*]furan (4a):
Acetate **4c** (1 g, 4.6 mmol) is hydrolysed by stirring 2.5 N aqueous NaOH (5 mL) at r.t. overnight. The mixture is then acidified with an excess of aqueous HCl and extracted with Et_2O (4 × 20 mL). The organic layer is washed with brine (6 × 10 mL) and dried (Na_2SO_4). The solvent is evaporated under normal pressure and the remaining product **4a** purified by sublimation at 90–100 °C/10 Torr; yield: 0.785 g (98%).

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