25. The Synthesis of Natural Acetylenic Compounds from *Eutypa lata* (Pers: F.) TUL.

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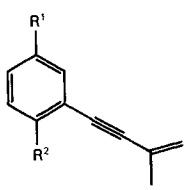
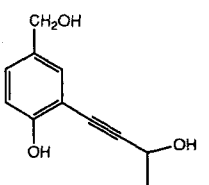
The synthesis of a series of novel acetylenic compounds **1–7**, isolated recently from the fungus *Eutypa lata*, is described. The crucial step is the coupling reaction between a protected aryl halogenide and the acetylenic chain as a cuprous acetylide (*Scheme 1*). A more efficient method using bis(triphenylphosphine)palladium dichloride ($[Pd(PPh_3)_2Cl_2]$) as catalyst was also carried out with success.

Introduction. – The fungus *Eutypa lata* also named *Eutypa armeniacae* is responsible for the dieback of vineyards (eutypiosis) observed during the last years in Switzerland, France, and many other countries [1]. In the course of our search for secondary metabolites with a phytotoxic activity in the culture medium of *Eutypa lata*, a series of new acetylenic compounds **1–7** were isolated [2] [3]. Compound **1** (= 4-hydroxy-3-(3-methylbut-3-en-1-ynyl)benzaldehyde), named eutypine, was found to be the most phytotoxic compound isolated [2] [3].





7

1 $R^1 = CHO$, $R^2 = OH$

2 $R^1 = CHO$, $R^2 = MeO$

3 $R^1 = COOH$, $R^2 = OH$

4 $R^1 = OH$, $R^2 = OH$

5 $R^1 = CH_2OH$, $R^2 = OH$

6 $R^1 = CH_2OH$, $R^2 = MeO$

To study the role played by eutypine **1** and the related compounds **2–7** in the pathogenesis of eutypiosis, more specific tests (by protoplast bioassay) are necessary. Thus, to acquire bigger quantities of material for the bioassay, compounds **1–7** were synthesized from the commercially available 4-hydroxybenzaldehyde.

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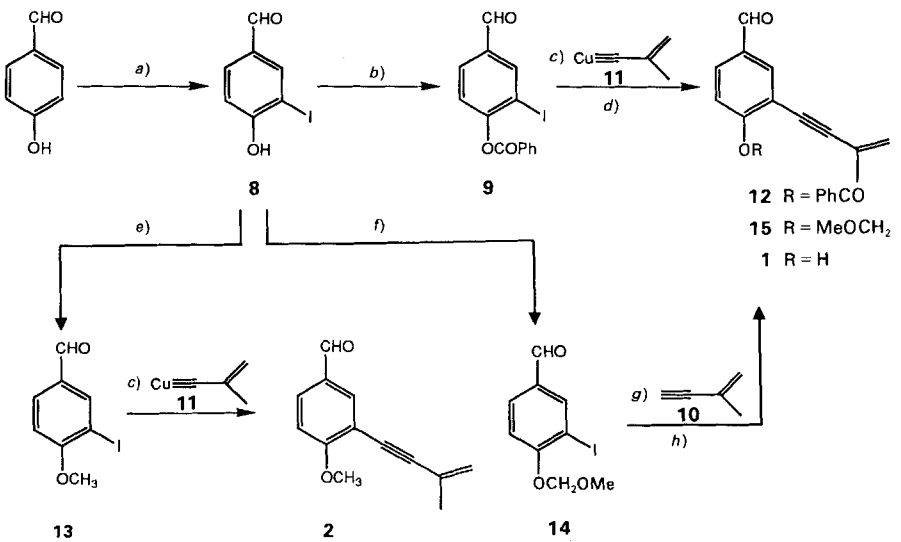
Results and Discussion. – The series of new acetylenic compounds is structurally similar to the previously reported frustulosin [4] and contains the same acetylenic chain, except for **7**. Retrosynthetic analysis suggested that **1** could be prepared by coupling the alkyne chain (as a cuprous acetylide) with an aryl halogenide [5]. Thus the iodo compound **8**, which was more reactive than the bromo or the chloro analogue, was prepared by iodination of 4-hydroxybenzaldehyde [6] (*Scheme 1*). However, direct coupling of **8** prior to protection of the phenol function produced cyclisation of the *ortho*-hydroxyacetylide leading to a benzofuran derivative[3]). Since eutypine (**1**) was relatively stable under basic conditions, we decided to protect the phenol as an ester (benzoate **9**) which was stable under the coupling conditions. Other protecting groups such as $MeOCH_2$, tetrahydro-2*H*-pyran-2-yl, Me_3Si, or (*t*-Bu)Me_2Si were unsuitable and led to the benzofuran derivative. The acetylenic chain 2-methylbut-1-en-3-yne (**10**) was prepared by

Scheme 1



a) I_2, KI, Me_2NH. *b*) PhCOCl, Et_3N, Et_2O. *c*) DMF, 120°. *d*) EtOH, 3% aq. NaOH soln. *e*) Me_2SO_4, K_2CO_3, acetone. *f*) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2. *g*) Et_2NH, $[Pd(PPh_3)_2Cl_2]$, CuI. *h*) AcOH/HCl.

dehydration of the commercially available 2-methylbut-3-yn-2-ol in Ac_2O/concentrated H_2SO_4 solution [7] and transformed to the cuprous acetylide **11** by using CuI in NH_4OH following *Atkinson*'s method [8]. Coupling of **9** and **11** was then accomplished in DMF for 3 h, affording compound **12**. The coupling temperature was crucial, the phenol protection (benzoate) being cleaved above 120° to give as the major product again the benzofuran derivative. Intermediate **12** was directly saponified without further purification to afford **1**. The overall yield was 20%, and large-scale synthesis was possible. Compound **2** was prepared in the same manner by coupling the iodo compound **13** with the cuprous acetylide **11**. The MeO group present in **2** could not serve as protecting group

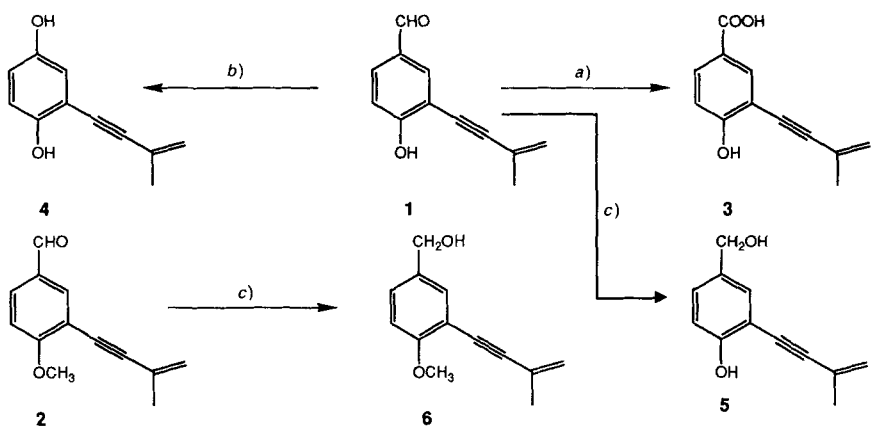
[3]) This type of benzofuran derivatives was also found in the culture media of *Eutypa lata*.

of the phenolic function in the synthesis of **1**, since **1** was unstable under the deprotection conditions. Compound **2** was also prepared from **1** by direct methylation with MeI.

A more efficient method of synthesizing **1** consisted in coupling the acetylenic chain **10** with an aryl halogenide in the presence of a catalyst, bis(triphenylphosphine)-palladium dichloride ($[Pd(PPh_3)_2Cl_2]$), in basic media [9]. In this case, the PhCO protecting group could not be used; it was replaced by the $MeOCH_2$ group which was easily introduced using dimethoxymethane in acidic media (**8** → **14**; *Scheme 1*). Subsequent coupling with **10** in the presence of $[Pd(PPh_3)_2Cl_2]$ in Et_2NH afforded, in good yield, **15** as a precursor of **1**. In acidic media, **15** was relatively unstable. Thus, hydrolysis of the $MeOCH_2$ group had to be performed under particularly mild conditions, *i.e.* in AcOH/concentrated HCl solution, leading to **1** in 55% overall yield.

Carboxylic acid **3** was obtained in good yield as white needles by oxidation of **1** using $NaClO_2$ in H_2O/dioxane solution [11] (*Scheme 2*). Under these conditions, Cl_2 was liberated. Thus, sulfamic acid was added to avoid chlorination of the product. However, some chlorohydrine derivative produced by chlorination of the double bond was also

Scheme 2

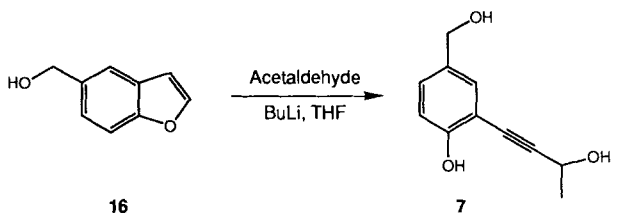


a) NH_2SO_3H, $NaClO_2$, dioxane/H_2O. *b*) H_2O_2, aq. KOH soln. *c*) $NaBH_4$, 1% aq. NaOH soln.

formed in low yield (< 5%). For the synthesis of hydroxyquinone **4**, **1** was treated with 3-chloroperbenzoic acid (*Baeyer-Villiger* reaction [12]) which resulted to the total degradation of **1**. However, using H_2O_2 in basic medium (*Dakin*'s reaction [13]), we obtained **4** in good yield. Compound **4** was identical to siccayne (described by *Pinault et al.* [14]) by spectroscopic means (NMR, MS). Diol **5** was obtained in quantitative yield by reduction of **1** using $NaBH_4$. The same procedure was applied to the reduction of **2** to afford **6**.

Triol **7** could not be prepared by coupling iodo compound **9** with the corresponding acetylenic chain (but-3-yn-2-ol), because the cuprous acetylide was unstable. By protecting the alcohol group of but-3-yn-2-ol with a tetrahydro-2*H*-pyran-2-yl group, the cuprous acetylide became more stable, but it was not reactive enough for coupling. Because of the high coupling temperature required, we only observed cyclisation to a benzofuran derivative (see above). However, the reversed reaction (opening of the benzo-

Scheme 3



16 **7**

furan ring) was possible [15] and studied in our laboratory [16]. Thus, alkylation of benzofuran **16**[4]) by acetaldehyde followed by ring-opening in the presence of the strong base BuLi yielded 53% of **7** (*Scheme 3*).

NMR and GC/MS comparison of the synthetic compounds **1–7** with the corresponding natural products confirmed their established structures. These compounds could be synthesized in large scale and are presently being tested for their phytotoxicity.

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Experimental Part

General. All commercially available chemical reagents were used without further purification. All reactions were followed by TLC: aluminium sheets silica gel *60 F_{254}* (*Merck*). Prep. column chromatography (CC): silica gel (*Merck 60*, 0.063–0.200 mm). M.p.: *Gallenkamp MFB-595-010M*. FT-IR [cm^{-1}]: *Perkin-Elmer 1720X*; KBr disks, unless otherwise indicated. ^{1}H-NMR: *Bruker AMX 400*; δ in ppm using TMS as internal standard, J in Hz. EI-MS: positive mode; *Nermag-R-3010* spectrometer. The microanalyses were done at the Laboratory for Organic Chemistry of ETH, Zurich.

4-Hydroxy-3-iodobenzaldehyde (**8**). To a soln. of commercial 4-hydroxybenzaldehyde (24.4 g, 0.2 mol) in 30% aq. Me_2NH, an aq. soln. of I_2 (40.6 g, 0.16 mol) and KI (50 g, 0.3 mol) was added dropwise at r.t. The mixture was stirred for 3 h, then cooled to 0°, acidified with 10% aq. HCl soln., and extracted with Et_2O. The org. layer was washed with 1% aq. $NaHSO_3$ soln., then with 5% aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated, and the residue purified by CC (CH_2Cl_2): **8** (28.8 g, 58%). M.p. 116–117°. FT-IR: 3300–3100 (OH), 1667, 1593, 1567, 1506, 1494, 1408, 1294, 1217, 1190, 1152, 1138, 890, 825. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.80 (*s*, CHO); 8.23 (*d*, J = 1.9, H–C(2)); 7.79 (*dd*, J = H–C(6)); 7.11 (*d*, J = 8.3, H–C(5)); 6.50 (br. *s*, OH). EI-MS: 248 (100, M^+), 247 (95, $[M-H]^+$), 219 (18), 92 (32), 63 (30).

4-(Benzoyloxy)-3-iodobenzaldehyde (**9**). To a soln. of **8** (6 g, 24 mmol) and Et_3N (3.7 g, 37 mmol) in dry Et_2O, an Et_2O soln. of benzoyl chloride (3.7 g, 26.5 mmol) was added dropwise at r.t. After 30 min, the soln. was filtered, washed with 0.5% aq. HCl soln., twice with 2% aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated, and the residue recrystallised in CH_2Cl_2/ligroine: **9** (7.3 g, 83%). M.p. 96°. FT-IR: 3060, 2855, 1745, 1700, 1590, 1565, 1475, 1450, 1375, 1270, 1245, 1215, 1185, 1170, 1060, 1020, 890, 815. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.97 (*s*, CHO); 8.41 (*d*, J = 1, H–C(2)); 8.28 (*m*, H–C(2′), H–C(6′)); 7.95 (*dd*, H–C(6)); 7.60–7.80 (*m*, H–C(3′), H–C(4′), H–C(5′)); 7.50 (*d*, J = 8, H–C(5)). EI-MS: 352 (1, M^+), 105 (100, $C_6H_5CO^+$), 77 (40, $C_6H_5^+$).

3-Iodo-4-methoxybenzaldehyde (**13**). To a soln. of **8** (5 g, 20 mmol) in dry acetone (100 cm^3) was added anh. K_2CO_3 (10 g, 72 mmol) and Me_2SO_4 (1.9 g, 15 mmol). The mixture was stirred for 3 h at r.t., then diluted with H_2O, and concentrated under vacuum. The aq. layer was extracted with Et_2O, the org. layer washed successively with 1% aq. NaOH soln. and sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated, and the residue purified by CC (CH_2Cl_2): **13** (4.2 g, 80%). M.p. 103°. FT-IR: 3010, 2970, 2935, 2830, 1675, 1650, 1590, 1565, 1490, 1440, 1310, 1275, 1255, 1180, 1155, 1045, 1015, 885, 825. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.82 (*s*, CHO); 8.30 (*d*, J = 2, H–C(2)); 7.85 (*dd*, H–C(6)); 6.92 (*d*, J = 9, H–C(5)); 3.97 (*s*, MeO). EI-MS: 262 (100, M^+), 261 (74, $[M-H]^+$), 119, 77.

[4]) Compound **16** was prepared in our laboratory in five steps from salicylaldehyde in 12% overall yield [16].

3-Iodo-4-(methoxymethoxy)benzaldehyde (**14**). To a soln. of **8** (10 g, 0.04 mol) and $CH_2(OMe)_2$ (20 equiv., 72 ml) in dry CH_2Cl_2 (100 ml) was added P_2O_5 (35 g) portionwise. After 2 h, more P_2O_5 (20 g) was added. The mixture was stirred for 5 h (complete disappearance of **8**). The mixture was then diluted with CH_2Cl_2, washed with 1N aq. NaOH and sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated. The yellow residue was used in the next step without purification. CC (CH_2Cl_2) yielded pure **14** (9.3 g, 80%). M.p. 66–67°. FT-IR: 3050, 2960, 2900, 2840, 1682, 1589, 1489, 1455, 1440, 1417, 1371, 1310, 1249, 1199, 1161, 1140, 1082, 1038, 1013, 973, 925. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.84 (*s*, CHO); 8.31 (*d*, J = 1.8, H–C(2)); 7.82 (*dd*, H–C(6)); 7.17 (*d*, J = 8.3, H–C(5)); 5.34 (*s*, CH_2); 3.52 (*s*, Me). EI-MS: 292 (10, M^+), 231 (5), 219 (5), 45 (100).

2-Methylbut-1-en-3-yne (**10**). A soln. of Ac_2O (50 g, 0.49 mol) and conc. H_2SO_4 (2 g) was added dropwise to 2-methylbut-3-yn-2-ol at 50°. Compound **10** was purified by distillation (11.4 g, 72%). B.p. 32–33°. n_D^{20} = 1.411 ([7]: 1.4099). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.39–5.29 (2*t*, C=CH_2); 2.87 (*s*, CH≡C); 1.90 (*t*, Me). EI-MS: (100, M^+), 65 (50, [M – H^+]), 63, 51, 50, 40, 39.

Copper(I) 3-Methylbut-3-en-1-yn-1-ide (**11**). To a soln. of CuI (8 g, 42 mmol) in 25% aq. NH_4OH soln. (100 ml), $NH_2OH \cdot HCl$ (200 mg) was added until the soln. was light blue. Then **10** (2.3 g, 34 mmol) in EtOH (10 ml) was added and the mixture stirred vigorously for 15 min and poured into H_2O (600 ml; → yellow precipitate). After 10–15 min, the mixture was filtered and the precipitate washed with H_2O and then EtOH and dried: **11** (2.2 g, 50%).

4-(Benzoyloxy)-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (**12**). Under N_2, **9** (2.0 g, 5.7 mmol) and **11** (1.45 g, 11.4 mmol) in dry DMF (50 ml) were heated at 110–120° for 3 h. The soln. was then concentrated by distillation under vacuum and AcOEt added. The insoluble Cu^I-salt was filtered off and the org. layer washed twice with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated to give a brown oil which was used without further purification for the next reaction. CC (CH_2Cl_2/hexane) gave pure **12** (0.64 g, 39%). EI-MS: 290 (5, M^+), 105 (100, $C_6H_5CO^+$), 77 (40, $C_6H_5^+$).

4-Hydroxy-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (= *Eutypine*; **1**). *a*) To an EtOH soln. (40 ml) of **12** (0.6 g) was added 3% aq. NaOH soln. (20 ml). After stirring for 2 h, the soln. was diluted with H_2O, concentrated under vacuum, and washed with Et_2O. The aq. layer was then acidified with 5% aq. HCl soln. and extracted with AcOEt. The org. layer was washed with 2% aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. The residual oil was purified by CC (CH_2Cl_2) to give **1** (120 mg, 62%). White needles. M.p. 76–77°. FT-IR: 3500–3100 (OH), 2959, 2922, 2852, 1670, 1600, 1567, 1496, 1435, 1375, 1321, 1295, 1265, 1251, 1143, 920, 831. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.85 (*s*, CHO); 7.89 (*d*, J = 1.8, H–C(2)); 7.79 (*dd*, H–C(6)); 7.08 (*d*, J = 8.5, H–C(5)); 6.39 (br. *s*, OH); 5.49–5.42 (2*s*, C=CH_2); 2.03 (*s*, Me). EI-MS: 186 (100, M^+), 185 (80, [M – H]$^+$), 157 (50, [M – CHO]$^+$), 128, 77. Anal. calc. for $C_{12}H_{10}O_2$ (186.21): C 77.40, H 5.41; found: C 77.10, H 5.26.

b) To a soln. of **15** (see below; 2.4 g, 0.01 mol) in AcOH (60 ml) were added five drops of 12N HCl. The soln. was stirred at r.t. under N_2 for 8 h and then poured slowly to sat. aq. $NaHCO_3$ soln. and extracted with Et_2O. The org. layer was washed several times with sat. aq. $NaHCO_3$ soln. and extracted again with 1N aq. NaOH soln. The aq. layer which contained **1** was then acidified with 5% aq. HCl soln. and extracted with Et_2O. The org. layer was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated. The residual oil was purified by CC (CH_2Cl_2): **1** (1.52 g, 78%). White needles.

4-(Methoxymethoxy)-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (**15**). A mixture of **14** (1.6 g, 0.006 mol), 2-methylbut-1-en-3-yne (**10**; 3 equiv., 1.1 g), [Pd(PPh_3)$_2Cl_2$] (0.01 equiv., 40 mg), and CuI (0.01 equiv., 11 mg) in Et_2NH (40 ml) was stirred overnight under N_2 at r.t. The mixture was then diluted with Et_2O, washed twice with 5% aq. HCl, twice with sat. aq. NaCl, dried ($MgSO_4$), and evaporated. The residual yellow oil was submitted to CC (silica gel): **15** (1.07 g, 85%). Pale-yellow oil. FT-IR (NaCl, film): 2958, 2922, 2829, 1697, 1595, 1573, 1496, 1444, 1430, 1371, 1311, 1246, 1154, 1124, 1114, 1083, 977, 818. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.87 (*s*, CHO); 7.94 (*d*, J = 2.1, H–C(2)); 7.78 (*dd*, H–C(6)); 7.23 (*d*, J = 8.6, H–C(5)); 5.45–5.35 (2*s*, C=CH_2); 5.33 (*s*, CH_2O); 3.53 (*s*, MeO); 2.01 (*s*, Me). EI-MS: 230 (20, M^+), 215 (15, [M – Me]$^+$), 199 (20), 128 (40), 45 (100).

4-Methoxy-3-(3-methylbut-3-en-1-ynyl)benzaldehyde (**2**) was prepared by the same route as **1** by coupling **13** with **11**. Yield 50%. M.p. 49–50°. FT-IR: 3095, 2950, 2840, 1695, 1595, 1575, 1500, 1460, 1440, 1300, 1260, 1130, 1120, 1020, 905, 815. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.86 (*s*, CHO); 7.94 (*d*, J = 1.8, H–C(2)); 7.82 (*dd*, H–C(6)); 6.99 (*d*, J = 8.5, H–C(5)); 5.45–5.35 (2*m*, C=CH_2); 3.97 (*s*, MeO); 2.02 (*s*, Me). EI-MS: 200 (100, M^+), 159 (40, [M – C_3H_5]$^+$), 128 (50, [M – $C_3H_4O_2$]$^+$), 43 (45, $C_3H_7^+$).

4-Hydroxy-3-(3-methylbut-3-en-1-ynyl)benzoic Acid (**3**). To **1** (0.2 g, 1.07 mmol) in dioxane/H_2O 3:2 (50 ml) was added sulfamic acid (0.6 g, 6.2 mmol) and $NaClO_2$ (0.96 g, 0.85 mmol). After 1 h stirring at r.t., $NaHCO_3$ (2 g) was added and the soln. concentrated and washed with AcOEt, acidified with 5% aq. HCl soln., and extracted with AcOEt. The org. layer was dried ($MgSO_4$) and evaporated. CC (CH_2Cl_2/AcOEt/AcOH 7:3:1): **3** (170 mg, 79%). White needles. M.p. 112°. FT-IR: 3470, 3410, 2925, 2855, 1685, 1610, 1580, 1495, 1420, 1320, 1280, 1220, 1170,

1120, 1100, 910, 840. ^{1}H-NMR (400 MHz, $CDCl_3$): 10.90 (br. *s*, COOH); 8.15 (*d*, *J* = 0.9, H–C(2)); 8.01 (*dd*, H–C(6)); 7.02 (*d*, *J* = 8.5, H–C(5)); 5.49–5.41 (2*m*, C=CH_2); 2.03 (*s*, Me). EI-MS: (100, M^+), 185 (30, $[M - OH]^+$), 157 (20, $[M - COOH]^+$), 128 (10), 51 (10).

2-(3-Methylbut-3-en-1-ynyl)benzene-1,4-diol (= *Siccayne*; **4**). To a soln. of **1** (0.28 g, 5 mmol) in aq. KOH soln. (20 ml), 3% aq. H_2O_2 soln. (5 ml) was added at r.t. under vigorous stirring. After 18 h, the aq. soln. was washed with Et_2O, acidified with 5% aq. HCl soln., and extracted with AcOEt. The org. layer was washed with 0.2% aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. CC (CH_2Cl_2) gave pure **4** (150 mg, 86%). M.p. 115° ([14]: 114–116°). FT-IR: 3500–3100 (OH), 2920, 1615, 1450, 1375, 1235, 1210, 1190, 1160, 1110, 990, 925, 890. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.79 (*m*, H–C(3), H–C(5), H–C(6)); 5.45–5.35 (2*m*, *J* = 0.5, C=CH_2); 4.91 (br. *s*, OH); 2.00 (*m*, *J* = 0.5, Me). EI-MS: 174 (100, M^+), 173 (30, $[M - H]^+$), 159 (30, $[M - Me]^+$), 147 (20), 131 (20), 115 (15), 103 (10), 91, 77.

4-Hydroxy-3-(3-methylbut-3-en-1-ynyl)benzyl Alcohol (**5**). To **1** (0.186 g, 1 mmol) in 1% aq. NaOH soln. (25 ml) was added dropwise a 10% aq. NaOH soln. (2 ml) of $NaBH_4$ (50 mg, 1.3 mmol). After 2 h, the mixture was diluted with AcOEt and acidified with 5% aq. HCl soln. The org. layer was then washed with aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated, and the residue purified by CC (CH_2Cl_2/AcOEt 9:1): **5** (179 mg, 95%). White needles. M.p. 63–65°. FT-IR: 3600–3100 (OH), 2955, 2890, 2200, 1715, 1610, 1510, 1430, 1375, 1320, 1290, 1240, 1180, 1120, 1010, 985, 815. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 (*d*, *J* = 1, H–C(2)); 7.23 (*dd*, H–C(6)); 6.92 (*d*, *J* = 8, H–C(5)); 5.43–5.35 (2*m*, *J* = 0.5, C=CH_2); 4.58 (*s*, CH_2OH); 2.01 (*m*, *J* = 0.5, Me). EI-MS: 188 (100, M^+), 171 (60, $[M - OH]^+$), 131, 91, 77.

4-Methoxy-3-(3-methylbut-3-en-1-ynyl)benzyl Alcohol (**6**). As described for **5**, **6** was prepared by reduction of **2**. Yield 90%. FT-IR: 3500–3200 (OH), 2930, 2840, 2190, 1670, 1605, 1500, 1460, 1420, 1385, 1280, 1255, 1180, 1160, 1130, 1030, 895, 815. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.46 (*d*, *J* = 1, H–C(2)); 7.28 (*dd*, H–C(6)); 6.89 (*d*, *J* = 9, H–C(5)); 5.45–5.33 (2*m*, *J* = 0.5, C=CH_2); 4.62 (*s*, CH_2OH); 3.91 (*s*, MeO); 2.02 (*dd*, *J* = 0.5, Me); 1.70 (br. *s*, OH). EI-MS: 202 (100, M^+), 201 (20, $[M - H]^+$), 185 (10), 161(10), 91, 77.

4-Hydroxy-3-(3-hydroxybut-1-ynyl)benzyl Alcohol (**7**). To 5-(hydroxymethyl)benzofuran (**16**; 0.9 g, 6 mmol) in dry THF (30 ml) was added 1.6M BuLi/hexane (8 ml, 12 mmol) at 0°. After 1 h, acetaldehyde (0.27 g, 6 mmol) was added and the mixture stirred for 1 h. Again, 1.6M BuLi/hexane (4 ml, 6 mmol) was added and stirred at r.t. for 3 h. The soln. was then quenched with aq. NH_4Cl soln. and concentrated under vacuum. The aq. layer was extracted with Et_2O and the org. layer extracted with 2% aq. NaOH soln. The aq. layer was then acidified with 5% aq. HCl soln. and extracted with AcOEt, the org. phase dried and evaporated, and the residue purified by CC (CH_2Cl_2): **7** (0.61 g, 53%). ^{1}H-NMR (400 MHz, CD_3OD): 7.27 (*d*, *J* = 2, H–C(2)); 7.15 (*dd*, H–C(6)); 6.80 (*d*, *J* = 8, H–C(5)); 4.70 (*q*, *J* = 7, C*H*(OH)Me); 4.46 (*s*, CH_2OH); 1.49 (*d*, *J* = 7, Me). EI-MS: 192 (30, M^+), 177 (100, $[M - Me]^+$), 91 (70), 84 (40).

REFERENCES

[1] A. Bolay, W. J. Moller, *Rev. Swiss Vitic. Arboric. Horticol.* **1977,** *9,* 241; M. V. Carter, A. Bolay, *Phytopath. Z.* **1972,** *75,* 187; M. C. Mauro, V. Valiant, P. Tey-Rulh, Y. Mathieu, J. Fallot, *Am. J. Enol. Vitic.* **1988,** *39,* 200.

[2] J. M. Renaud, G. Tsoupras, R. Tabacchi, *Helv. Chim. Acta* **1989,** *72,* 929.

[3] P. De Angelis, Thesis, University of Neuchâtel, 1990.

[4] M. S. R. Nair, M. Anchel, *Phytochmistry* **1977,** *16,* 390.

[5] C. E. Castro, R. D. Stephens, *J. Org. Chem* **1963,** 2163; G. Posner, in 'Organic Reactions', J. Wiley & Sons, New York, 1972, Vol. 19, pp. 253–361.

[6] J. H. Barnes, E. T. Borrows, J. Elks, B. Hems, A. G. Long, *J. Chem. Soc.* **1950,** 2824.

[7] A. A. Petrov, K. V. Mingelava, B. S. Kupin, *Dokl. Akad. Nauk SSSR* **1958,** *123,* 258.

[8] R. E. Atkinson, R. F. Curtis, J. A. Taylor, *J. Chem. Soc. (C)* **1967,** 578.

[9] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975,** 4467.

[10] K. Fuji, S. Nakano, E. Fujita, *Synthsis* **1975,** 276.

[11] B. O. Lindgreen, T. Nilson, *Acta Chem. Scand.* **1973,** *27,* 888.

[12] I. M. Godfrey, M. V. Sargent, J. A. Elix, *J. Chem. Soc., Perkin Trans. 1* **1974,** 1353.

[13] L. Syper, *Synthesis* **1989,** 167.

[14] M. Pinault, Y. Frangin, J.-P. Genet, H. Zamarlik, *Synthesis* **1990,** 935.

[15] V. Prey, H. Pieh, *Monatsh. Chem.* **1949,** *80,* 790; H. Emmert, *Ber. Dtsch. Chem. Ges.* **1917,** *50,* 31; C. D. Hurd, G. L. Oliver, *J. Am. Chem. Soc.* **1959,** *81,* 2795; H. G. Gilman, D. S. Melstrom, *ibid.* **1948,** *70,* 1655; A. Gabert, H. Normant, *C. R. Hebd. Séances. Acad. Sci., Paris* **1959,** *233,* 1407.

[16] T. Zesiger, Thesis, University of Neuchâtel, 1991.