

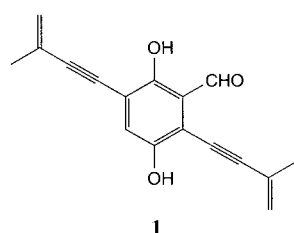
The Synthesis of Natural Acetylenic Compounds from *Stereum hirsutum*

by Abdellatif Fkyerat, Guy-Marie Dubin, and Raffaele Tabacchi*

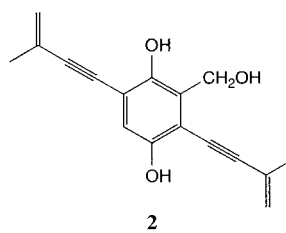
Institut de Chimie de l'Université de Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel

The regioselective synthesis of two new acetylenic compounds, sterehirsutinal (**1**) and sterehirsutinol (**2**), isolated recently from culture medium of the fungus *Stereum hirsutum*, is reported.

Introduction. – *Stereum hirsutum* is a basidiomycete involved in esca, one of the most destructive diseases of grapevine [1]. To find an alternative control method as efficient as the highly toxic sodium-arsenite treatment, the search for a pathogenically active secondary metabolite was necessary. From the culture medium of *Stereum hirsutum*, a series of new acetylenic compounds was isolated [2]. The structure of sterehirsutinal (**1**), and sterehirsutinol (**2**) were elucidated by spectroscopic analysis and by comparison with the biogenetically related frustulosin. Thus, to confirm their structures and to obtain higher quantities of material for bioassays, **1** and **2** were synthesized starting from the commercially available hydroquinone (**3**).



Stere-hirsutinal

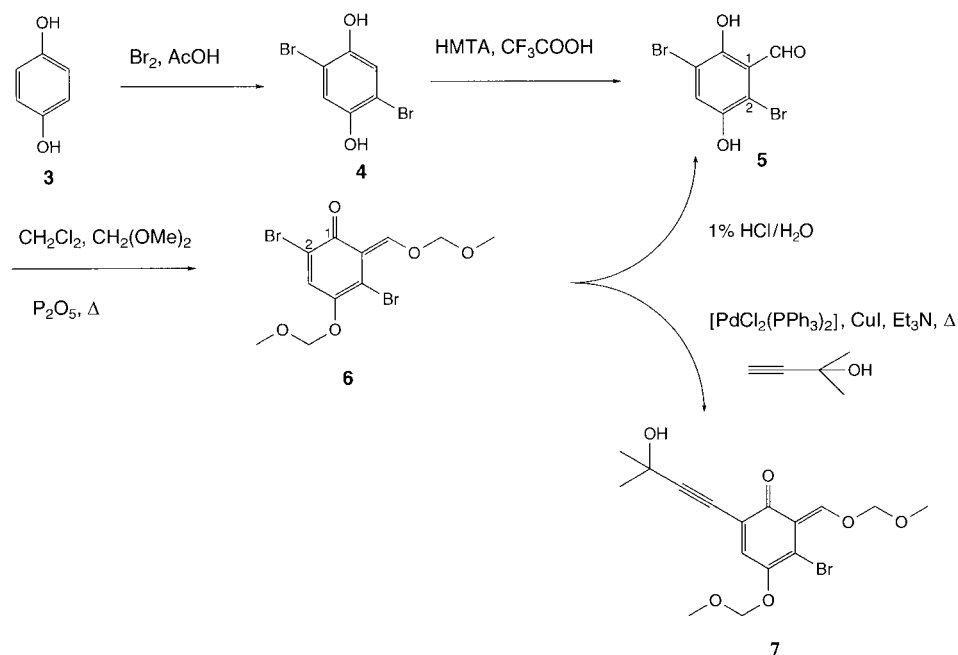


Stere-hirsutinol

Results and Discussion. – A similar synthetic strategy applied previously for sicayne [3], eutypine [4], and frustulosin [5], compounds containing the same alkenynyl side chain, was followed for the synthesis of **1** and **2**. *retro*-Synthetic analysis suggested that **1** could be prepared by coupling the alkynyl chain with a dihalogenobenzene derivative. The latter compound could be obtained in two steps from hydroquinone (**3**). Thus, the 2,5-dibromobenzene-1,4-diol (**4**) was prepared by bromination of **3** with Br₂ in AcOH (*Scheme 1*). Compound **4** has been prepared previously from benzoquinone in HBr and Br₂ [6], but this method gave a mixture of the mono and dibromo derivatives, which were difficult to separate. The carboxaldehyde function was introduced into **4** by *Duff's* reaction [7], with hexamethylenetetramine (HMTA) in trifluoroacetic acid (→ **5**).

To avoid the cyclization reaction leading to a benzofurane derivative [3–5], the phenolic OH groups of **5** had to be protected. Because of the instability of the *ortho*-

Scheme 1

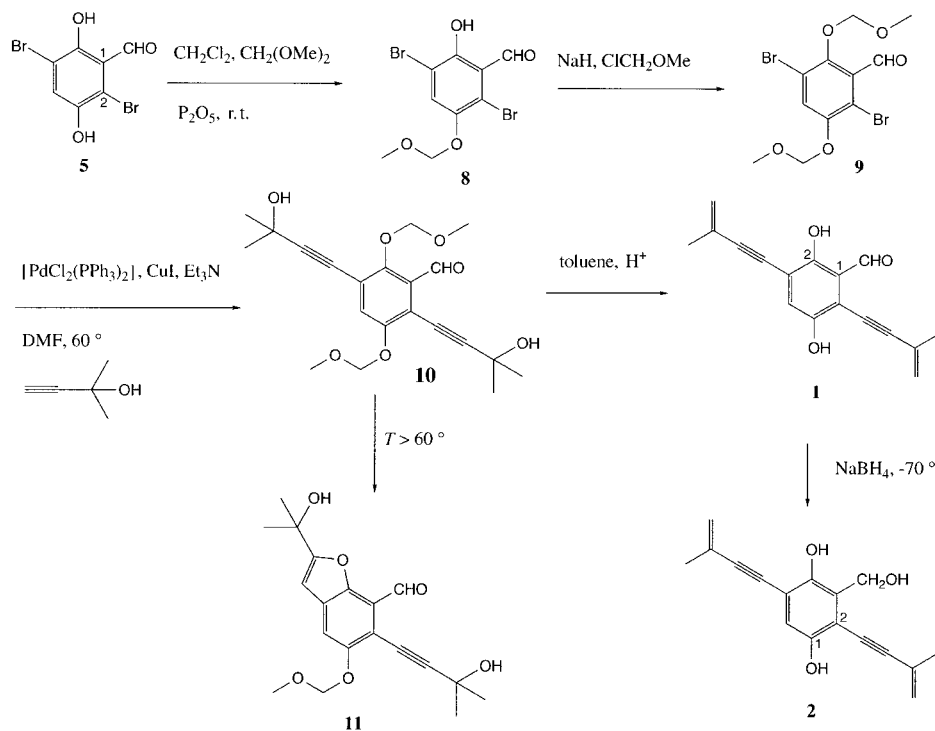


OH acetylenic compounds under acidic conditions, the appropriate OH-protecting group was the methoxymethyl (MOM) group which could be hydrolyzed under mild conditions. Under standard protection conditions (dimethoxymethane and P_2O_5 in CH_2Cl_2 at room temperature), only one of the two phenolic OH groups ($\text{OH}-\text{C}(3)$) of **5** reacted to give the mono-protected compound **8** (see below, *Scheme 2*). At higher temperature, a second MOM group was introduced, however, selectively at the aldehyde moiety due to the delocalization of the $\text{CH}=\text{O}$ bond, to give the enone **6**. Under the same conditions, 2,5-dihydroxybenzaldehyde could be protected at the two phenolic positions. This result suggests that the steric hindrance of the Br-atoms influences the reaction at the aldehyde group; such an unexpected reaction has previously been described for the intramolecular cyclization in the synthesis of heterocycles [8].

Since the enone **6** could be easily hydrolyzed to give back the starting material **5**, we decided to continue the synthesis of **1** and **2** via this intermediate. The alkynyl side chain was introduced easily at position 6 of **6** ($\rightarrow$ **7**); unfortunately, no alkylation of **6** occurred at position 3, even at high temperature (90°) (*Scheme 1*). This result forced us to modify the experimental conditions for the protection of the phenolic OH groups of **5**. Thus, **5** was first protected at position 3 in acidic medium to give **8** and then at position 6 in basic medium to give **9** (*Scheme 2*). The dibromobenzaldehyde **9** then underwent the desired coupling reactions with 2-methylbut-3-yn-2-ol in the presence of dichlorobis(triphenylphosphine)palladium ($[\text{PdCl}_2(\text{PPh}_3)_2]$) and Et_3N in DMF at 60° for 3 h to give the bis(hydroxyalkynyl)benzaldehyde **10**. Temperature and reaction time were crucial in the coupling step. At higher temperature or after more than 3 h at

60°, benzofurancarboxaldehyde **11** was obtained as the major product. The aldehyde group of **10** seems to play the role of catalyst for the deprotection of the adjacent phenolic group, which cyclized to **11**. Finally, the difficult deprotection and dehydration of **10** was accomplished in a one-pot reaction in anhydrous toluene at 60°, in the presence of TsOH and molecular sieves, to give sterehirsutinal (**1**) with moderate yield. Sterehirsutinol (**2**) was obtained in quantitative yield by reduction of **1** with NaBH₄ at –70°. Coupling of aldehyde **9** with 2-methylbut-3-yn-2-ol, followed by dehydration of the intermediate **10**, was preferred to the direct coupling of **9** with 2-methylbut-1-en-3-yne, because of the instability and low boiling point of the eneyne [9].

Scheme 2



We would like to thank Dr. S. Claude for his assistance in NMR spectroscopy. The financial support from the Swiss National Science Foundation (grant No. 20.46920.96) and OFES, European project (grant 95.0064 UE:FAIR1-CT95-0654), are gratefully acknowledged.

Experimental Part

General. All commercially available chemical reagents were used without further purification. CH₂Cl₂ was distilled over CaH₂ and toluene over P₂O₅. M.p.: *Gallenkamp M FB-595-010M*. TLC: Aluminium sheets coated with silica gel 60 F₂₅₄ (Merck). Prep. column chromatography (CC): silica gel (0.063–0.200 mm; 60 Merck). FT-IR: Perkin-Elmer 1720X; samples were measured as thin films on NaCl disks, unless otherwise indicated; in cm^{–1}. ¹H-NMR: Bruker AMX 400; δ in ppm relative to SiMe₄ as internal standard, J in Hz. MS: electron-impact

ionization (EI) or desorption chemical ionization (DCI); *Nermag-R-30-10* spectrometer. The microanalyses were performed at the Laboratory for Organic Chemistry, ETH Zurich.

2,5-Dibromobenzene-1,4-diol (4). A soln. of Br₂ (16 g, 0.1 mol) in AcOH (10 ml) was added dropwise to a soln. of hydroquinone (= benzene-1,4-diol; **3**; 5.5 g, 0.05 mol) in AcOH (40 ml). The mixture was stirred at r.t. for 1 h, H₂O was added, and the brown solid was filtered and crystallized from H₂O: **4** (4.8 g, 36%). White needles. M.p. 190–191°. FT-IR: 3268 (OH), 3094, 3050, 2784, 2076, 1703, 1638, 1515, 1423, 1234, 1222, 1196, 1116, 1061, 863. ¹H-NMR (400 MHz, CDCl₃): 7.62 (s, arom. H); 6.88 (s, OH). ¹³C-NMR (CDCl₃): 146.91 (C(1), C(4)); 119.18 (C(3), C(6)); 108.56 (C(2), C(5)). Anal. calc. for C₆H₄Br₂O₂: C 26.90, H 1.50, Br 59.65; found: C 26.85, H 1.60, Br 59.92.

2,5-Dibromo-3,6-dihydroxybenzaldehyde (5). A mixture of **4** (2.68 g, 0.01 mol), hexamethylenetetramine (= 1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane; 1.4 g, 0.01 mol) in CF₃COOH (20 ml) was heated under reflux for 16 h. The solvent was evaporated and the residual oil diluted in H₂O (1000 ml) and heated at 60° for 6 h. The mixture was extracted with AcOEt (5 × 100 ml), the org. layer washed with sat. NaCl soln. (10 × 100 ml), dried (MgSO₄), and evaporated, and the residual brown oil crystallized from AcOEt/hexane: **5** (2.3 g, 78%). Yellow solid. FT-IR: 3456, 3067, 2922, 2855, 1646, 1437, 1261, 1233, 1181, 1143, 852, 721, 560, 506, 496. ¹H-NMR (400 MHz, CDCl₃): 12.04 (s, OH); 10.16 (s, CHO); 7.81 (br. s, OH); 7.38 (s, arom. H). ¹³C-NMR (CDCl₃): 208.16; 197.07 (CHO); 153.84; 146.58; 127.92 (C(4)); 117.02; 112.21; 110.33. EI-MS: 296 (100, M⁺), 266, 39, 07, 187, 157, 131, 88, 73, 70, 61.

2,5-Dibromo-6-hydroxy-3-(methoxymethoxy)benzaldehyde (8). To a soln. of **5** (1.5 g, 5 mmol) and CH₂(OMe)₂ (excess, 10 ml) in dry CH₂Cl₂ (10 ml), P₂O₅ (3.5 g) was added portionwise. After 2 h, more P₂O₅ (2 g) was added and stirred until **5** disappeared (TLC monitoring). The mixture was diluted with CH₂Cl₂, washed with 1N aq. NaOH and sat. aq. NaCl soln., dried (MgSO₄), and evaporated. The yellow solid was purified by CC (AcOEt/hexane 1:9): yellow **8** (1.34 g, 80%). FT-IR: 3443 (OH), 3082, 3002, 2942, 2829, 1650, 1473, 1436, 1417, 1401, 1291, 1272, 1250, 1205, 1161, 1149, 1087, 1017, 942, 919, 879, 822, 760, 733. ¹H-NMR (CDCl₃): 12.25 (s, OH); 10.34 (s, CHO); 7.64 (s, H–C(4)); 5.16 (s, CH₂); 3.53 (s, Me). ¹³C-NMR (CDCl₃): 197.55 (CHO); 155.50; 147.10; 129.07 (C(4)); 117.80; 117.04; 110.58; 96.39 (CH₂); 56.64 (Me). DCI-MS: 354 ([M + NH₄]⁺), 340 (M⁺), 310, 275, 185, 157, 133, 88, 73, 70, 61. Anal. calc. for C₉H₈Br₂O₄: C 31.80, H 2.37, Br 47.01; found: C 31.96, H 2.48, Br 47.01.

2,5-Dibromo-4-(methoxymethoxy)-6-[(methoxymethoxy)methylene]cyclohexa-2,4-dien-1-one (6) was prepared as described for **8**, but at reflux temp. in CH₂Cl₂. Yield: 75%. ¹H-NMR (CDCl₃): 7.41 (s, H–C(3)); 5.40 (s, CH); 5.37 (d, J = 13.2, 1 H, CH₂OCH=C(6)); 5.33 (d, J = 13.2, 1 H, CH₂OCH=C(6)); 5.17 (d, J = 6.80, 1 H, CH₂O–C(4)); 5.15 (d, J = 6.80, 1 H, CH₂O–C(4)); 3.63 (s, Me); 3.52 (s, Me). ¹³C-NMR (CDCl₃): 175.93 (CO); 148.45; 145.48; 122.50; 121.65 (C(3)); 112.73; 109.35; 96.01 (CH₂); 95.83 (CH); 84.55 (CH₂); 56.46 (Me); 55.81 (Me). Anal. calc. for C₁₁H₁₂Br₂O₅: C 34.40, H 3.15, Br 41.61; found: C 34.40, H 3.21, Br 41.52.

5-Bromo-2-(3-hydroxy-3-methylbut-1-ynyl)-4-(methoxymethoxy)-6-[(methoxymethoxy)methylene]cyclohexa-2,4-dien-1-one (7) was prepared as described for **10**. Yield: 81%. FT-IR: 3442, 2981, 2933, 2832, 1739, 1589, 1486, 1458, 1411, 1381, 1350, 1323, 1285, 1245, 1208, 1195, 1155, 1099, 1059, 1031, 998, 961, 881, 813. ¹H-NMR (CDCl₃): 7.20 (s, H–C(3)); 5.37 (s, CH); 5.34 (d, J = 16.1, 1 H, CH₂OCH=C(6)); 5.29 (d, J = 16.1, 1 H, CH₂OCH=C(6)); 5.16 (d, J = 9.7, 1 H, CH₂O–C(4)); 5.11 (d, J = 9.7, 1 H, CH₂O–C(4)); 3.61 (s, Me); 3.51 (s, Me); 1.61 (s, 2 Me). ¹³C-NMR (CDCl₃): 171.16 (CO); 148.94; 147.73; 121.74; 121.20; 111.15; 99.37; 95.99 (CH); 95.85 (CH₂); 84.24 (CH₂); 65.69; 65.50; 56.40 (Me); 55.70 (Me); 31.33 (2 Me).

2,5-Dibromo-3,6-bis(methoxymethoxy)benzaldehyde (9). To a soln. of **8** (1.35 g, 4 mmol) in DMF (20 ml) at 0° under N₂, a 60% NaH suspension in mineral oil (0.21 g, 4.4 mmol) was added portionwise. After 10 min, chloromethyl methyl ether (0.334 ml, 4.4 mmol) was added dropwise and stirred at r.t. for 2 h. The soln. was poured into H₂O and extracted with AcOEt, the org. layer washed with sat. NaCl soln., dried (MgSO₄), and evaporated, and the residual yellow oil submitted to CC (silica gel, hexane/AcOEt 95:5): **9** (74%). White solid. FT-IR: 2996, 2963, 2938, 2871, 2834, 1771, 1699, 1660, 1575, 1537, 1485, 1463, 1453, 1438, 1381, 1278, 1237, 1207, 1157, 1090, 996, 939, 920, 887, 868, 827. ¹H-NMR (CDCl₃): 10.23 (s, CHO); 7.56 (s, H–C(4)); 5.24 (s, CH₂); 5.06 (s, CH₂); 3.62 (s, Me); 3.51 (s, Me). ¹³C-NMR (CDCl₃): 190.02 (CHO); 151.21; 149.86; 131.31; 123.72 (C(4)); 117.78; 113.60; 101.53 (CH₂); 95.64 (CH₂); 58.26 (Me); 56.62 (Me). EI-MS: 384 (68, M⁺), 353 (35), 338 (100), 324 (24). Anal. calc. for C₁₁H₁₂Br₂O₅: C 34.40, H 3.15, Br 41.61; found: C 34.60, H 3.21, Br 41.44.

2,5-Bis(3-hydroxy-3-methylbut-1-ynyl)-3,6-bis(methoxymethoxy)benzaldehyde (10). A soln. of **9** (192 mg, 0.5 mmol), 2-methylbut-3-yn-2-ol (0.200 ml, 2 mmol), [PdCl₂(PPh₃)₂] (70 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and Et₃N (0.28 ml, 2 mmol) in DMF (2 ml) was heated at 60° under N₂ for 1 h. The mixture was then diluted in H₂O and extracted with AcOEt, the org. layer washed twice with 2% aq. HCl soln. and twice with sat. NaCl soln., dried (MgSO₄), and evaporated, and the residual brown oil submitted to CC (silica gel, hexane/

AcOEt 1:1): **10** (140 mg, 72%). Brown oil. FT-IR: 3407 (OH), 2981, 2935, 2832, 1699, 1649, 1585, 1462, 1376, 1324, 1271, 1237, 1205, 1156, 1072, 1036, 1009, 982, 956, 925, 878. ¹H-NMR (CDCl₃): 10.40 (s, CHO); 7.29 (s, H–C(4)); 5.17 (s, CH₂); 5.16 (s, CH₂); 3.56 (s, Me); 3.50 (s, Me); 2.86 (s, OH); 1.62 (s, Me); 1.60 (s, Me). ¹³C-NMR (CDCl₃): 190.01 (CHO); 154.29; 154.21; 130.95; 124.43 (C(4)); 118.56; 115.50; 106.35; 100.85; 100.59 (CH₂); 99.65; 95.48 (CH₂); 74.95; 65.48; 58.09 (MeO); 56.43 (MeO); 31.13 (2 Me); 31.09 (2 Me).

6-(3-Hydroxy-3-methylbut-1-ynyl)-2-(1-hydroxy-1-methylethyl)-5-(methoxymethoxy)benzofuran-7-carboxaldehyde (**11**) was obtained as major product under the conditions described for **10**, but at higher temp. Yield: 60%. FT-IR: 3449 (OH), 2981, 2934, 1690, 1645, 1607, 1450, 1369, 1261, 1224, 1205, 1153, 1118, 1072, 1046, 1015, 998, 969, 934, 848. ¹H-NMR (CDCl₃): 10.61 (s, CHO); 7.46 (s, H–C(4)); 6.53 (s, H–C(3)); 5.24 (s, CH₂); 3.56 (s, MeO); 1.69 (s, 4 Me). ¹³C-NMR (CDCl₃): 190.66 (CO); 167.18; 154.03; 147.58; 130.53; 120.93; 114.04 (C(4)); 105.34; 99.86 (C(3)); 96.13 (CH₂); 74.52; 68.64; 65.77; 60.39; 56.37; 31.19 (2 Me); 28.35 (2 Me).

2,5-Dihydroxy-3,6-bis(3-methylbut-3-en-1-ynyl)benzaldehyde (**1**). A soln. of **10** (223 mg, 0.57 mmol) in toluene (5 ml) was stirred at 60° for 5 h in the presence of a catalytic amount of TsOH. The soln. was diluted with AcOEt, washed with sat. NaCl soln., dried (MgSO₄), and evaporated, and the residue purified by CC (silica gel, AcOEt/hexane 1:4): **1** (25 mg, 25%). ¹H-NMR (CDCl₃): 11.70 (s, OH); 10.30 (s, CHO); 7.27 (s, arom. H); 5.42 (m, OH, 2 CH₂); 2.06 (t, Me); 2.02 (t, Me). ¹³C-NMR (CDCl₃): 196.47 (CHO); 157.84, 150.22 (C(2), C(5)); 127.17 (C(4)); 126.08; 125.52 (CH₂); 124.01 (CH₂); 118.40; 115.43; 111.61; 105.91; 98.71; 82.91; 23.95 (Me); 23.86 (Me).

3-(Hydroxymethyl)-2,5-bis(3-methylbut-3-en-1-ynyl)benzene-1,4-diol (**2**). A soln. of **1** (7 mg, 0.03 mmol) in MeOH (5 ml) was cooled at –70°, and excess of NaBH₄ was added portionwise. After 10 min, the yellow color disappeared, and the soln. was diluted with H₂O/10% HCl soln. 5:1. The resulting soln. was extracted with AcOEt (3 × 10 ml), the extract washed with NaCl, dried (MgSO₄), and evaporated, and the residue purified by CC (silica gel, hexane/AcOEt 4:1): **2** (6 mg, 86%). White solid. ¹H-NMR (CDCl₃): 6.91 (s, arom. H); 6.32 (s, OH–C(arom.)); 5.41 (m, CH₂); 5.31 (m, CH₂); 4.91 (d, CH₂OH); 2.41 (t, CH₂OH); 2.01 (m, 2 Me). ¹³C-NMR (CDCl₃): 149.70; 148.98; 126.31; 126.03; 125.75; 123.63 (CH₂); 123.31 (CH₂); 116.30 (C(6)); 111.74; 110.26; 102.75; 98.49; 82.06; 79.83; 60.66 (CH₂OH); 23.28 (2 Me). EI-MS: 268 (54, M⁺), 250 (100), 235 (7), 221 (7), 207 (8), 193 (6), 179 (25), 178 (32).

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