Reactions of Ketene Acetals; 12[1]. A Regiospecific Synthesis of Anthragallols

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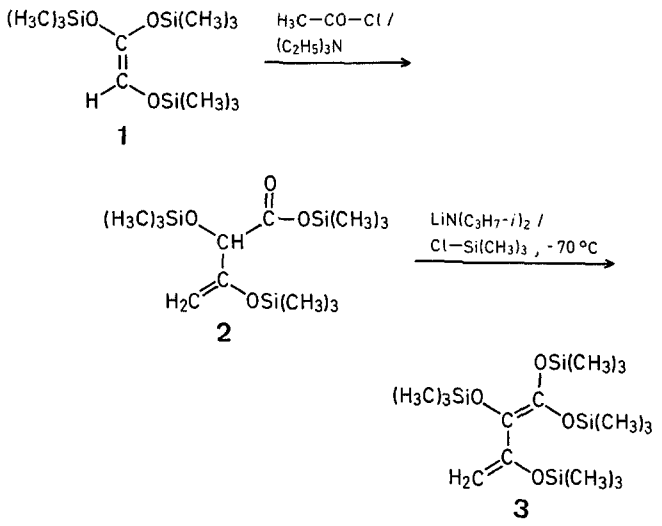
Anthraquinones bearing three adjacent hydroxy (or methoxy) groups are widely distributed in nature and have been isolated from such diverse sources as higher plants (mainly Rubiaceae), fungi, and insects[2]. Some of these substances are available by synthesis using, as a rule, one of the various Friedel-Crafts procedures. Nevertheless, these condensations are devoid of regiochemical control, generally give complex mixtures of products in low yield, and sometimes require difficultly accessible substrates.

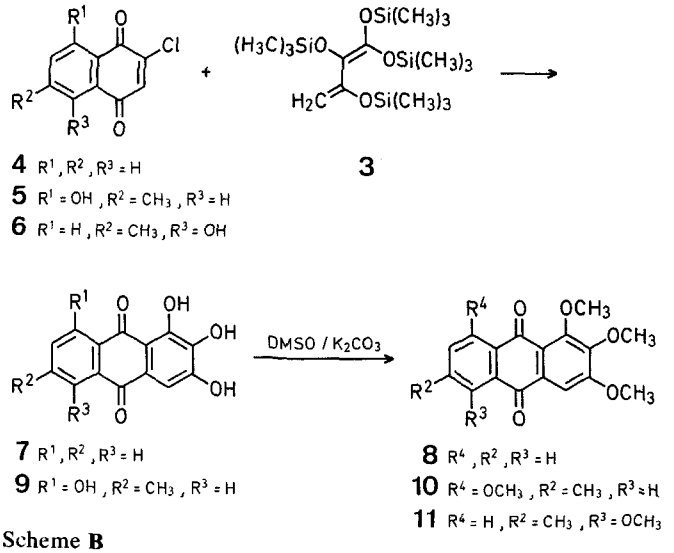
Recent applications of vinylketene mixed acetals to the regiospecific formation of polycyclic quinones[1] suggest an analogous approach in this case. The reaction[3] of ketene, prepared *in situ* from acetyl chloride and triethylamine, with the new ketene acetal, tris[trimethylsiloxy]ethene[4] (**1**) provided the convenient intermediate trimethylsilyl 2,3-bis[trimethylsiloxy]buten-3-oate (**2**) in excellent yield (89–93%). This ester, when treated with lithium diisopropylamide and chlorotrimethylsilane, then gave the required vinylketene acetal, 1,1,2,3-tetrakis[trimethylsiloxy]-1,3-butadiene (**3**; 84–87% yield) (Scheme **A**).



Scheme **A**

Diene **3** reacts rapidly with benzoquinones such as 2,6-dichloro- and 2-chloro-5-methoxy-benzoquinone, however numerous attempts to aromatize the adducts under various conditions, in general, result in extensive decomposition. In only one case could a 5% yield of a naphthoquinone, 3-chloro-5,6,7-trimethoxy-naphthoquinone, be obtained after methylation of the crude product, and it appears that trihydroxynaphthoquinones are too sensitive to the reaction conditions devised up until now.

Reactions of diene **3** with naphthoquinones were more successful, and these inherently less reactive substrates usually give the best results when condensations were carried out in the absence of solvent. In this way chloronaphthoquinone (**4**) gave an 82%



Scheme **B**

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yield of anthragallol (**7**) (or, after methylation of the crude product, 83% of the corresponding trimethyl ether **8**) (Scheme **B**). The regiospecificity of the process was shown by reacting the diene **3** with 3-chloro-7-methyljuglone[1] (**5**). The product obtained was identified as 7-hydroxyemodin (**9**) by comparison with the spectral and physical data[5] available for this compound.

Extension of the foregoing principle was established by the synthesis of copareolatin (as its tetramethyl ether **11**) from the appropriate 2-chlorojuglone **6**. This is the first time that a naturally occurring anthraquinone is prepared by this approach using a substrate in which the *peri*-hydroxy group and the halogen exert opposing effects. It was expected from well established electronic considerations[6], that the reaction should be more difficult than with the isomeric 3-halojuglones, but comparison of this condensation with the behaviour of ketene dimethyl acetal towards 2- and 3-bromojuglones[7] allowed the prediction, eventually confirmed that only copareolatin would be formed (Scheme **B**).

Trimethylsilyl 2,3-Bis[trimethylsiloxy]but-3-enoate (2):
Acetyl chloride (11.9 g, 0.15 mol) in anhydrous ether (100 ml) is added slowly (during 2.5 h) at room temperature to a solution of tris[trimethylsiloxy]ethene (**1**; 43.8 g, 0.15 mol) and dry triethylamine (15.2 g, 0.15 mol) in the same solvent (100 ml). The reaction mixture is stirred for 3 h, filtered, and evaporated. Distillation of the residue under vacuum gives the $\beta\gamma$-unsaturated ester **2**; yield: 46.8 g (93%); b.p. 88–94 °C/1.8 torr.

$C_{13}H_{30}O_4Si_3$	calc.	C 46.66	H 9.04
(334.6)	found	46.36	9.13

I.R. (film): ν = 1734, 1716 (C=O); 1638 (C=C); 838 cm^{-1} (Si—C).

^{1}H-N.M.R. (90 MHz, $CDCl_3$): δ = 0.16, 0.22, 0.30 [3 s, 3×9H, 1,2,3-OSi$(CH_3)_3$]; 4.25 (d, 1H, J = 1.7 Hz, 4-H); 4.45 (s, 1H, 2-H); 4.48 ppm (d, 1H, J = 1.7 Hz, 4-H).

1,1,2,3-Tetrakis[trimethylsiloxy]-1,3-butadiene (3):
To a solution of lithium diisopropylamide, prepared from 1.6 molar *n*-butyllithium (0.05 mol) in hexane (31 ml) and diisopropylamine (5.1 g, 0.05 mol) in anhydrous tetrahydrofuran (50 ml) at 4 °C (30 min), is added at −70 °C (during 50 min) trimethylsilyl 2,3-bis[trimethylsiloxy]but-3-enoate (**2**; 16.8 g, 0.05 mol) in tetrahydrofuran (50 ml). The solution is stirred at −70 °C for 30 min and the enolate quenched by addition of chlorotrimethylsilane (13.6 g, 0.125 mol) at −60 to −65 °C (10 min). After stirring at −65 °C for 30 min, the reaction mixture is allowed to come to room temperature, concentrated, and filtered. The solids are washed with dry ether (150 ml) and the combined filtrates evaporated. Upon distillation under vacuum, the residue gives diene **3**; yield: 17.7 g (87%); b.p. 76–78 °C/0.07 torr.

$C_{16}H_{38}O_4Si_4$	calc.	C 47.24	H 9.42
(406.8)	found	47.60	9.01

I.R. (film): ν = 1643, 1594 (diene); 845 cm^{-1} (Si—C).

^{1}H-N.M.R. (90 MHz, $CDCl_3$): δ = 0.13, 0.16, 0.18 [3 s, 9H, 18H, 9H, 1,1,2,3-OSi$(CH_3)_3$]; 4.23 (s, 1H, 4-H); 4.48 ppm (s, 1H, 4-H).

The substance can be kept unchanged at −15 °C for at least six months.

1,2,3-Trihydroxyanthraquinone (Anthragallol; 7):
A mixture of 2-chloronaphthoquinone (**4**; 0.772 g, 4.00 mmol) and the butadiene **3** (2.436 g, 6.00 mmol) is heated at 50 °C for 18 days (or at 100 °C for 36 h) and hydrolyzed by warming at 50 °C for a few minutes with a 1:1 mixture (40 ml) of tetrahydrofuran and 2% aqueous hydrochloric acid. The crude product is purified by chromatography on silica gel, deactivated by addition of 15% water (eluent: chloroform/ethyl acetate, 5:1); yield of **7**: 841 mg (82%); m.p. 308 °C (nitrobenzene) (Ref.[8], m.p. 310 °C; Ref.[9], m.p. 309–310 °C).

$C_{14}H_8O_5$	calc.	C 65.63	H 3.15
(256.2)	found	65.85	3.28

M.S.: m/e = 256 (M^+).

I.R. (Nujol): ν = 3450, 3370 (OH); 1653 (C=O); 1630 (chelated C=O); 1584 cm^{-1} (aryl).

U.V. (ethanol): λ_{max} = 239 sh (logε = 4.08); 245 (4.12); 286 (4.33); 410 nm (3.80).

Upon methylation of the crude product (dimethyl sulfate/potassium carbonate/acetone, 18 h), anthragallol trimethyl ether (**8**) is obtained directly by dry column chromatography on silica gel (eluent: benzene/ethyl acetate, 20:1); yield: 79–83%; m.p. 171–172 °C (acetone) (Ref.[10], m.p. 167–169 °C; Ref.[8], m.p. 167 °C).

$C_{17}H_{14}O_5$	calc.	C 68.45	H 4.73
(298.3)	found	68.72	4.84

M.S.: m/e = 298 (M^+).

I.R. (KBr): ν = 1665 (C=O); 1590, 1574 cm^{-1} (aryl).

U.V. (ethanol): λ_{max} = 239 (logε = 4.11); 245 (4.08); 276 (4.64); 350 nm (3.92).

^{1}H-N.M.R. (90 MHz, $CDCl_3$): δ = 3.99, 4.00, 4.03 (3 s, 3×3H, 1,2,3-OCH_3); 7.6–7.8 (m, 2H, 6,7-H), 7.67 (s, 1H, 4-H); 8.1–8.3 ppm (m, 2H, 5,8-H).

1,2,3,8-Tetrahydroxy-6-methylanthraquinone (7-Hydroxyemodin; 9):
A solution of 3-chloro-5-hydroxy-7-methylnaphthoquinone[1] (**5**; 223 mg, 1.00 mmol) and the butadiene **3** (913 mg, 2.25 mmol) in benzene (40 ml) is refluxed (2–5 d), evaporated, and the residue pyrolyzed at 110–115 °C for 1.5–3 h. After hydrolysis as described above (10 ml), the crude product is sublimed (270 °C/0.1 torr) to give the expected anthraquinone **9**; yield: 247 mg (86%); m.p. 295 °C (dec.) (methanol) [Ref.[5,11], m.p. 296–298 °C (dec.); Ref.[12], m.p. 294 °C (dec.)].

$C_{15}H_{10}O_6$	calc.	C 62.94	H 3.52
(286.2)	found	62.95	3.61

I.R. (Nujol): ν = 3380, 3160 (OH); 1660 (C=O); 1620 (br, chelated C=O); 1565 cm^{-1} (aryl).

U.V. (ethanol): λ_{max} = 216 (logε = 4.56); 254 (4.07); 289 (4.50); 430 nm (4.19).

^{1}H-N.M.R. (90 MHz, DMSO-d_6): δ = 2.28 (br. s, 3H, 6-CH_3); 6.98 (d, 1H, J = 1.5 Hz, 7-H); 7.17 (s, 1H, 4-H); 7.30 ppm (d, 1H, J = 1.5 Hz, 5-H).

Methylation of the foregoing crude product followed by dry column chromatography on silica gel (eluent: benzene/ethyl acetate, 20:1) gives 1,2,3,8-tetramethoxy-6-methylanthraquinone (**10**); yield: 222 mg (65%); m.p. 162–163 °C (methanol).

$C_{19}H_{18}O_6$	calc.	C 66.66	H 5.30
(342.3)	found	66.42	5.27

M.S.: m/e = 342 (M^+).

I.R. (KBr): ν = 1667 (C=O), 1594, 1572 cm^{-1} (aryl).

U.V. (ethanol): λ_{max} = 218 (logε = 4.51); 276 (4.54); 365 nm (3.99).

^{1}H-N.M.R. (90 MHz, $CDCl_3$): δ = 2.47 (s, 3H, 6-CH_3); 3.99, 4.02, 4.04 (3 s, 6H, 3H, 3H, 1,2,3,8-OCH_3); 7.06 (br. s, 1H, 7-H); 7.52 (s, 1H, 4-H); 7.58 ppm (br. s, 1H, 5-H).

2-Chloro-5-hydroxy-6-methylnaphthoquinone (6):
5-Hydroxy-6-methylnaphthoquinone (m.p. 107–108 °C from petroleum ether, b.p. 30–80 °C; Ref.[13], m.p. 108 °C), prepared from 8-chloro-5-hydroxy-6-methylnaphthoquinone[7] in 27% yield by the method of Bendz and Linberg[14], is acetylated (acetate, m.p. 145–146 °C from absolute ethanol) and chlorinated according to Thomson[6]. The addition – elimination in the presence of sodium acetate gives the 2-chlorojuglone **6**, after hydrolysis (ethanol/concentrated hydrochloric acid) and chromatography (CCl_4); yield: 36%; m.p. 158–159 °C (petroleum ether, b.p. 30–80 °C); [acetate, m.p. 137–139 °C (absolute ethanol)].

$C_{11}H_7ClO_3$	calc.	C 59.34	H 3.17	Cl 15.93
(222.6)	found	59.56	3.23	15.73

I.R. (KBr): ν = 1666 (C=O); 1630 (chelated C=O); 1583 cm^{-1} (aryl).

U.V. (ethanol): λ_{max} = 217 (logε = 4.23); 278 (3.55); 420 nm (3.55).

^{1}H-N.M.R. (90 MHz, $CDCl_3$): δ = 2.30 (s, 3H, 6-CH_3); 7.14 (s, 1H, 3-H); 7.52 (dd, 2H, J = 8.0 Hz, $\Delta\nu$ = 10.3 Hz, 7,8-H); 12.17 ppm (s, 1H, 5-OH).

1,2,3,5-Tetramethoxy-6-methylanthraquinone (Copareolatin Tetramethyl Ether; 11):

A mixture of 2-chloro-5-hydroxy-6-methylnaphthoquinone (**6**; 55 mg, 0.25 mmol) and the butadiene **3** (407 mg, 1.00 mmol) is stirred at 50 °C for 7 d. After hydrolysis and methylation as described above, copareolatin tetramethyl ether (**11**) is isolated by dry column chromatography on silica gel (eluent: benzene); yield: 75 mg (87%); m.p. 181–182 °C (methanol) (Ref.[15], m.p. 182–183 °C; 184–185 °C). Unfortunately an authentic sample of this substance was unavailable.

$C_{19}H_{18}O_6$	calc.	C 66.66	H 5.30
(342.3)	found	66.81	5.52

M.S.: $m/e = 342$ (M^+).

I.R. (KBr): $\nu = 1668$ (C=O); 1577 cm^{-1} (aryl).

U.V. (ethanol): $\lambda_{max} = 212$ ($\log \varepsilon = 4.31$); 277 (4.44); 354 (3.54); 360 nm (3.88).

^{1}H-N.M.R. (90 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3H, 6-CH_3); 3.91, 3.98, 3.99, 4.03 (4 s, 4 × 3H, 1,2,3,5-OCH_3); 7.55 (d, 1H, $J = 8.0$ Hz, 7-H); 7.64 (s, 1H, 4-H); 7.97 ppm (d, 1H, $J = 8.0$ Hz, 8-H).

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[1] Part 11: J. Savard, P. Brassard, *Tetrahedron Lett.* **1979**, 4911.
[2] R. H. Thomson, *Naturally Occurring Quinones*, 2nd Edn., Academic Press, London, New York, 1971, p. 367.
[3] M. W. Rathke, D. F. Sullivan, *Tetrahedron Lett.* **1973**, 1297.
[4] A. Wissner, *J. Org. Chem.* **44**, 4617 (1979).
[5] A. W. K. Chan, W. D. Crow, *Aust. J. Chem.* **19**, 1701 (1966).
[6] R. H. Thomson, *J. Org. Chem.* **16**, 1082 (1951).
[7] J. Banville, J.-L. Grandmaison, G. Lang, P. Brassard, *Can. J. Chem.* **52**, 80 (1974).
[8] L. H. Briggs, G. A. Nicholls, *J. Chem. Soc.* **1949**, 1241.
[9] A. R. Burnett, R. H. Thomson, *J. Chem. Soc.* [C] **1968**, 2437.
[10] A. G. Perkin, C. W. H. Story, *J. Chem. Soc.* **1929**, 1399.
[11] A. R. Mehendale, A. V. Rama Rao, K. Venkataraman, *Indian J. Chem.* **10**, 1041 (1972).
[12] H. J. Banks, D. W. Cameron, M. J. Crossley, *Aust. J. Chem.* **29**, 2231 (1976).
[13] T. J. Lillie, O. C. Musgrave, *J. Chem. Soc. Perkin Trans. 1* **1977**, 355.
[14] G. Bendz, G. Lindberg, *Acta Chem. Scand.* **24**, 1082 (1970).
[15] L. H. Briggs, G. A. Nicholls, R. M. L. Paterson, *J. Chem. Soc.* **1952**, 1718.