85 (100), 74 (13), 57 (56), 56 (62), 43 (20), 41 (57). The product was identical in all respects with a specimen prepared by epoxidation with MCPBA. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.52; H, 8.76.

Safrole oxide (10) was obtained by procedure A as a yellowish oil, which by distillation gave a colorless product: bp 111–112 °C (2 mm) [lit.[27] bp 116–118 °C (4 mm)]. It had spectra identical with those of an authentic sample prepared by a reported procedure.[27] Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.17; H, 5.74.

(*Z*)-17α,20-Epoxy-4-pregnen-3-one (11) was prepared by procedure A: mp 178–179 °C (EtOAc); $[\alpha]^{25}_D$ +105° (*c* 2, $CHCl_3$); IR (CH_2Cl_2) 3013, 2945, 2880, 1666, 1615, 1469, 1452, 1434, 1420, 1380, 1270, 1228, 889, 867 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.93 (s, 3 H, C-18 Me), 1.19 (s, 3 H, C-19 Me), 1.37 (d, *J* = 5.7 Hz, 3 H, C-21 Me), 2.98 (q, *J* = 5.7 Hz, 1 H, C_{20}-H), 5.73 (s, 1 H, C_4-H); MS, *m/e* (relative intensity) 314 M^+ (22), 270 (90), 149 (50), 122 (60), 95 (100), 93 (66), 79 (41), 67 (25), 55 (32), 43 (64). The product was identical in all respects with a specimen prepared by epoxidation with MCPBA. Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.25; H, 9.63.

By treatment with $LiAlH_4$ and subsequent oxidation with MnO_2,[11] **11** was converted to 17α-hydroxy-pregn-4-en-3-one (17-ethylepitestosterone): mp 151–153 °C (lit.[11] mp 152–153 °C); $[\alpha]^{20}_D$ +81° ($CHCl_3$) [lit.[11] $[\alpha]^{20}_D$ +81° ($CHCl_3$)].

(*E*)-4,5-Epoxydecane (12) was prepared by procedure A: bp 59–60 °C (1 mm); IR (neat) 2962, 2936, 2876, 2860, 1466, 1430, 1380, 1120, 951, 903, 879 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (m, 3 H), 0.96 (m, 3 H), 1.20–1.38 (m, 4 H), 1.38–1.64 (m, 8 H), 2.60–2.73 (m, 2 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.97, 19.44, 22.67, 25.83, 31.78, 34.33, 58.64, 58.80; MS, *m/e* (relative intensity) 156 M^+ (0.75), 138 (10), 113 (20), 99 (6), 95 (18), 85 (10), 71 (18), 67 (40), 57 (84), 55 (100), 43 (76), 41 (62). The product was identical in all respects with a specimen prepared by epoxidation with MCPBA. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 77.18; H, 13.16.

Registry No. **1b**, 112421-56-4; **2**, 69017-35-2; **3**, 112399-92-5; **4**, 2855-19-8; **5**, 2984-50-1; **6**, 286-20-4; **7**, 96-06-0; **8**, 598-09-4; **9**, 106-89-8; **10**, 7470-44-2; **11**, 14928-97-3; **12**, 56740-10-4; **13**, 96-09-3; **14**, 1689-70-9; **15**, 5076-20-0; **16**, 106-86-5; **17**, 5116-65-4; **18**, 106-87-6; H_3PO_4, 7664-38-2; $Na_2WO_4 \cdot H_2O$, 10213-10-2; *O*-acetyleugenol, 93-28-7; *n*-butyl 3-butenoate, 14036-56-7; 1-dodecene, 112-41-4; 1-octene, 111-66-0; cyclohexene, 110-83-8; 2,4,4-trimethyl-2-pentene, 107-40-4; methallyl chloride, 563-47-3; allyl chloride, 107-05-1; safrole, 94-59-7; (*Z*)-pregna-4,17(20)-dien-3-one, 51154-62-2; (*E*)-4-decene, 19398-89-1; styrene, 100-42-5; (*E*)-4-octene, 14850-23-8; tetramethylethylene, 563-79-1; 4-ethenyl-1-cyclohexene, 100-40-3; tungstic acid, 7783-03-1.

(27) Noller, C. R.; Kneeland, P. D. *J. Am. Chem. Soc.* **1946**, *68*, 201.

Notes

Regioselective Synthesis of 2- and 3-(Phenylthio)juglone Derivatives

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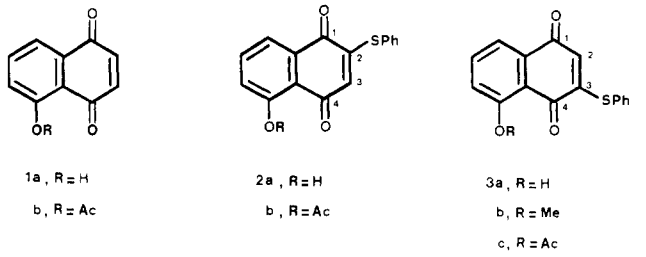
Regioisomeric (phenylthio)juglone derivatives **2**, **3**, and related compounds are useful synthons in several approaches to anthracyclinones.[1,2] Indeed, the utility of the phenylthio group (and corresponding sulfoxide) in this field of chemistry is well established, as an element directing the regiochemistry of the Diels–Alder reaction of such unsymmetrically substituted naphthoquinones,[2-4] and as a moiety temporarily preventing aromatization (through tautomerization) of the resulting adducts.[2] An efficient, highly regioselective method for the preparation of target compounds **2** and **3** is therefore required.

In 1951, Thomson claimed that the addition of thiophenol to juglone derivatives proceeds regioselectively, juglone (**1a**) giving the *3-substituted* product **3a**, and juglone acetate (**1b**), the *2-substituted* regioisomeric derivative **2b**.[5,6] However, in constrast with this early communication, the same author noted in 1960:[7] "The addition of toluene-*p*-thiol to juglone acetate is peculiar. As reported some years ago, it leads to the formation of 2-(*p*-tolylthio)juglone acetate. This has been successfully repeated, but recently this reaction has given predominantly the 3-isomer on several occasions!" More recently, Boeckman[1,4] and Kraus[2,3] applied the addition reaction of aromatic thiols on juglone (**1a**) and on juglone acetate (**1b**) to secure regiochemistry in approaches to anthracyclinone systems; in both cases the original observation of Thomson was confirmed.

In connection with our research in the anthracyclinone field,[8] we recently repeated Thomson's work. Surprisingly, these additions proved to be very erratic in our hands! Thus, when the addition reaction of thiophenol on juglone acetate (**1b**) was repeated 13 times, the 3-substituted isomer **3c** was predominantly obtained nine times and the 2-substituted regioisomer **2b**, four times; similarly the addition reaction of thiophenol on juglone (**1a**) was found to be nonreproducible (Scheme I) (see Experimental Section).

Scheme I



(1) Boeckman, R. K., Jr.; Delton, M. H.; Dolak, T. M.; Watanabe, T.; Glick, M. D. *J. Org. Chem.* **1979**, *44*, 4396.
(2) Kraus, G. A.; Walling, J. A. *Tetrahedron Lett.* **1986**, *27*, 1873.
(3) Kraus, G. A.; Woo, S. H. *J. Org. Chem.* **1986**, *51*, 114.
(4) Boeckman, R. K., Jr.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.
(5) Thomson, R. H. *J. Chem. Soc.* **1951**, 1237.
(6) Thomson, R. H. *J. Org. Chem.* **1951**, *16*, 1082.
(7) MacLeod, J. W.; Thomson, R. H. *J. Org. Chem.* **1960**, *25*, 36.
(8) Guingant, A.; d'Angelo, J. *Tetrahedron Lett.* **1986**, *27*, 3729.

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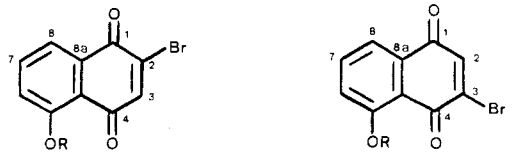
Scheme II



4a, R = H
b, R = Ac

5a, R = H
b, R = Me

In view of such disappointing results,[9] we were compelled to look for a more suitable method for the preparation of compounds **2** and **3**. In 1951, Thomson reported that 2-chlorojuglone reacts with *p*-thiocresol in the presence of pyridine, to lead to 2-(*p*-tolylthio)juglone[6] (and conversely, the 3-chloro isomer, the 3-thio derivative). However, at that time, neither the regioselectivity of this substitution process (for a discussion, see ref 7) nor the structural assignment of the products was unambiguously established. We therefore examined the substitution reaction, by reaction of benzenethiolate ion, with 2-bromojuglone acetate (**4b**)[10] and 3-bromojuglone methyl ether (**5b**)[11] (Scheme II), both materials being easily and efficiently obtained, in a fully regioselective manner, starting from 1,5-diacetoxynaphthalene and 1,5-dimethoxynaphthalene respectively. This method proved to be very efficient and general: as expected, displacement of the bromide by the phenylthio group was completely regioselective, both substitution reactions taking place, according to an ipso attack, exclusively at the carbon center bearing the bromine atom[12] (**4b** → **2b** and **5b** → **3b**).

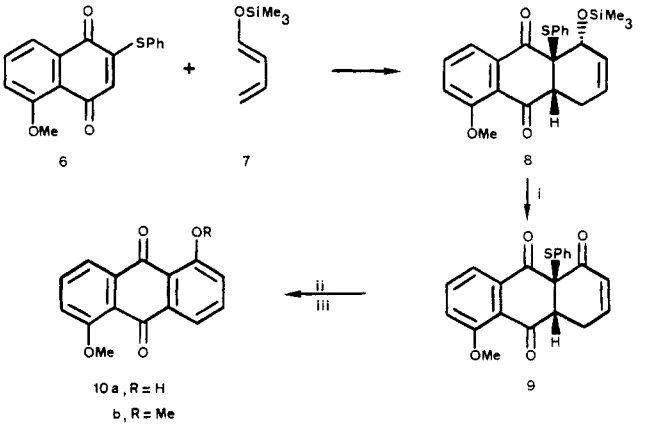
The positional assignment of the phenylthio substituent found in regioisomeric series products **2** and **3** was rigorously established, by NMR data analysis of pair compounds **2a**, **3a**. For this purpose, the heteronuclear ^{13}C–^{1}H long range coupling constants method, developed for juglone derivatives, was successfully applied. Indeed, previous ^{13}C NMR studies by Sammes et al.[13] on various 2- and 3-aminojuglones showed that the C4 carbonyl resonance appears downfield relative to C1 and that the associated coupling constants $^{3}J_{CH}$ are greater than $^{2}J_{CH}$. Structural assignments for the 2- and 3-substituted juglones could therefore easily be deduced from the multiplicity of the carbonyl signals; thus, recently, this method has been sucessfully applied to the unambiguous regiochemical characterization of 2- and 3-hydroxyjuglones.[14] We first examined the known pair 2- and 3-bromojuglone (**4a**[15] and **5a**[16]) and found that their ^{13}C NMR spectra were, according to the above-mentioned method, in complete agreement with the proposed structures (Table I). With these results in hand, we then examined (phenylthio)juglones **2a** and **3a**; in both cases, the proposed structural assignments were fully confirmed by the multiplicity of the carbonyl signals, as shown in Table I.

Table I. ^{13}C NMR Spectral Data of Juglone Derivatives[a]

juglone derivatives	C1	C4	C8a
2-bromo (**4a**)[b]	177.1 (br dd) J_{C1-H3} = 9 Hz J_{C1-H8} = 4 Hz	187.4 (br s)	130.8 (br d) J_{C8a-H7} = 8 Hz
3-bromo (**5a**)[b]	181.5 (br d) J_{C1-H8} = 4 Hz	182.9 (d) J_{C4-H2} = 9 Hz	131.8 (br dd) J_{C8a-H7} = 7.3 Hz J_{C8a-H2} = 4 Hz
2-phenylthio (**2a**)[c]	181.2 (br d) J_{C1-H3} = 9 Hz	187.2 (s)	
3-phenylthio (**3a**)[c]	181.1 (br s)	187.0 (d) J_{C4-H2} = 9 Hz	

[a] δ (Me_4Si as internal standard); multiplicity in the proton-coupled spectrum; coupling constants lower than 2 Hz are not taken into account in this analysis. [b] $CDCl_3$, 63 MHz; assignments are in agreement with those made by Heinzman and Grunwell.[10] [c] $CDCl_3$, 20 MHz.

Scheme III[a]



6 7 8 9

10a, R = H
b, R = Me

[a] (i) Jones reagent; (ii) $AlCl_3$; (iii) MeI, Ag_2O.

Furthermore, the proposed regiochemistry was supported by a chemical correlation, made as follows, starting from 2-(phenylthio)juglone (**2a**). Diels–Alder cycloaddition of methoxy derivative **6** (obtained by methylation of compound **2a**) with 1-(trimethylsiloxy)butadiene (**7**) gave the only tricyclic adduct **8**, which was then oxidized to enone **9** (Scheme III). The regiochemistry of the cycloaddition process was determined at this stage, from ^{1}H NMR data.[17] Finally, Lewis acid promoted aromatization of enone **9** led to 1-hydroxy-5-methoxyanthraquinone (**10a**), which was converted into 1,5-dimethoxyanthraquinone (**10b**), the latter being unequivocally identified by comparison with an authentic sample.

Addition of two other reagents to juglone derivatives was also found to be nonregioselective. Thus, in close analogy to the findings reported in this paper, Sammes noted in 1978 that, contrary to the original claim, addition of amines to juglone led to various mixtures of 2- and 3-amino derivatives.[13] Similarly, Parker reported in 1981 that the addition of hydrazoic acid to juglone methyl ether is nonregioselective, while the related substitution reaction, using azide ion, on 2- and 3-bromojuglone methyl ethers proceeds regioselectively[18] (the substitution taking place, once again, at the carbon center bearing the bromine

(9) In agreement with Thomson,[7] we believe that two competitive addition mechanisms (radical contra ionic) are probably implicated in such uncontrolled changes of regioselectivity.
(10) Heinzman, S. W.; Grunwell, J. R. *Tetrahedron Lett.* **1980**, *21*, 4305.
(11) Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153.
(12) In contrast, thiophenol reacts with 2-bromo-1,4-naphthoquinone to give 2-bromo-3-(phenylthio)-1,4-naphthoquinone via a reductive addition process followed by air oxidation: Miyaki, K.; Ikeda, N. *Yakugaku Zasshi* **1953**, *73*, 961; *Chem. Abstr.* **1954**, *48*, 10702c).
(13) Castillo, G.; Ellames, G. J.; Osborne, A. G.; Sammes, P. G. *J. Chem. Res., Miniprint* **1978**, 836.
(14) Barre, G.; Hocquaux, M.; Jacquet, B.; de Min, M.; Maurette, M. T.; Oliveros, E. *Tetrahedron Lett.* **1986**, *27*, 6197.
(15) 2-Bromojuglone was obtained by hydrolysis of the corresponding acetate **4b**: Thomson, R. H. *J. Org. Chem.* **1948**, *13*, 377.
(16) 3-Bromojuglone was prepared from juglone, by using Rapoport's procedure.[11]
(17) Moreover, for obvious chemical reasons, the regioisomeric cycloadduct would lead, after oxidation, to a very unstable compound, aromatizing spontaneously through a facile tautomerization process.
(18) Parker, K. A.; Sworin, M. E. *J. Org. Chem.* **1981**, *46*, 3218.

atom). To conclude, the addition of thiophenol to juglone derivatives is too erratic to be safely used for synthetic purposes; the indirect method proposed here—substitution of bromojuglone derivatives by means of the benzenethiolate ion—should be preferred, as it is completely regioselective and gives better yields.

Experimental Section

General Methods. Melting points were recorded on a Kofler bench. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded on Varian EM-390 (90 MHz) or Brücker AM-250 (250 MHz) spectrometers. ^{13}C NMR spectra were recorded on Varian FT 80A (20 MHz) or Brücker AM-250 (63 MHz) spectrometers. The observed chemical shifts are given from tetramethylsilane. Mass spectra were measured by using a Kratos MS-30 mass spectrometer (70 eV, direct introduction). Elemental analyses were performed by the Service d'Analyses du CNRS, 69390 Vernaison. Commercially available juglone and thiophenol (Aldrich Chemical Co.) were used. When carefully purified (recrystallized juglone, bidistilled thiophenol), these reagents gave also erratic results in the following additions.

Addition of Thiophenol to Juglone (1a). Thomson's procedure[5] was followed. The following **2a**/**3a** ratios (by 90-MHz ^{1}H NMR spectral analysis of the crude products) were observed: 17/83, 28/72, 50/50.

Addition of Thiophenol to Juglone Acetate (1b). Thomson's procedure[6] (which was also used by Kraus[2]) was followed. The following **2b**/**3c** ratios (determined from 90-MHz ^{1}H NMR spectra of the crude mixtures) were obtained (experimental conditions in parentheses): (EtOH, reflux) 8/92, 8/92, 15/85, 17/83, 23/77, 27/73, 31/69, 75/25; (MeOH reflux) 82/18, 39/61; (MeOH and catalytical amounts of AIBN, reflux) 82/18; (CH_2Cl_2/MeOH, 25 °C) 80/20; (AcOH, 50°C) 32/68.

5-Acetoxy-3-(phenylthio)-1,4-naphthoquinone (3c). Pure compound **3c** was obtained by recrystallization of previous mixtures in ethanol: yellow-orange needles; mp 156 °C; IR ($CDCl_3$) 3150, 2960, 1765, 1665, 1650, 1595, 1565, 1195 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 6.04 (s, 1 H), 7.28 (dd, J = 1.5, 7.8 Hz, 1 H), 7.50 (m, 5 H), 7.68 (t, J = 7.8 Hz, 1 H), 7.95 (dd, J = 1.5, 7.8 Hz, 1 H). Anal. Calcd for $C_{18}H_{12}O_4S$: C, 66.65; H, 3.73; S, 9.88. Found: C, 66.67; H, 3.81; S, 9.82.

5-Acetoxy-2-(phenylthio)-1,4-naphthoquinone (2b). A solution of 1.3 mL (12.2 mmol) of thiophenol and 0.68 g (12.2 mmol) of potassium hydroxide in 10 mL of methanol was added dropwise, under nitrogen, to a solution of 3.6 g (12.2 mmol) of 5-acetoxy-2-bromo-1,4-naphthoquinone (**4b**)[10] in 50 mL of THF and 15 mL of methanol. The resulting mixture was stirred for 2.5 h at room temperature and concentrated under reduced pressure, and the residue was taken up in 250 mL of methylene chloride and washed with 100 mL of water. The aqueous layer was then extracted with 50 mL of methylene chloride. The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized (ethanol), yielding 3.97 g (75%) of naphthoquinone **2b**: yellow-orange needles; mp 188 °C; IR ($CDCl_3$) 1752, 1660, 1637, 1192 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 5.94 (s, 1 H), 7.32 (dd, J = 1.5, 7.8 Hz, 1 H), 7.50 (m, 5 H), 7.69 (t, J = 7.8 Hz, 1 H), 8.07 (dd, J = 1.5, 7.8 Hz, 1 H). Anal. Calcd for $C_{18}H_{12}O_4S$: C, 66.65; H, 3.73; S, 9.88. Found: C, 66.50; H, 3.73; S, 9.89.

5-Hydroxy-2-(phenylthio)-1,4-naphthoquinone (2a). A suspension of 0.86 g (2.65 mmol) of acetate **2b** in 150 mL of ethanol and 43 mL of 12 N hydrochloric acid was refluxed for 15 min after complete dissolution, cooled, poured into 300 mL of water, and then extracted twice with methylene chloride (300 and 100 mL). The combined organic layers were washed with 70 mL of water and dried over magnesium sulfate, and the solvent was removed under reduced pressure, yielding 0.75 g (100%) of naphthoquinone **2a**: orange-red solid; mp 143 °C (EtOH); IR ($CDCl_3$) 3500–2700, 3150, 2950, 1655, 1625, 1560, 1225 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.98 (s, 1 H), 7.17 (dd, J = 2.4, 7.2 Hz, 1 H), 7.40–7.65 (m, 7 H), 12.02 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) off-resonance δ 114.6 (s), 119.7 (d), 125.0 (d), 127.2 (s), 127.6 (d), 130.4 (d), 130.6 (d), 131.5 (s), 135.6 (d), 158.0 (s), 161.3 (s), 181.2 (s), 187.2 (s), proton coupled (see Table I). Anal. Calcd for $C_{16}H_{10}O_3S$: C, 68.07; H, 3.57; S, 11.36. Found: C, 68.28; H, 3.59; S, 11.26.

5-Hydroxy-3-(phenylthio)-1,4-naphthoquinone (3a). This compound was obtained in the same way as **2a**, by starting from acetate **3c**: orange-red solid; mp 155 °C (EtOH) (lit.[5] mp 153 °C); IR ($CDCl_3$) 3500–2700, 3150, 2950, 1630, 1562, 1290, 1270 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.03 (s, 1 H), 7.15 (dd, J = 2.4, 7.2 Hz, 1 H), 7.40–7.65 (m, 7 H), 11.68 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) off-resonance δ 114.6 (s), 119.3 (d), 123.8 (d), 127.0 (s), 128.9 (d), 130.5 (d), 130.7 (d), 132.2 (s), 135.7 (d), 137.1 (d), 156.3 (s), 161.8 (s), 181.1 (s), 187.0 (s), proton coupled (see Table I).

5-Methoxy-2-(phenylthio)-1,4-naphthoquinone (6). Silver oxide (3.3 g, 14.2 mmol) and 2.2 mL (35 mmol) of methyl iodide were added to a solution of 1.0 g (3.5 mmol) of naphthoquinone **2a** in 40 mL of methylene chloride. The resulting suspension was stirred in the dark for 15 h and filtrated on Celite and the filtrate concentrated under reduced pressure. The remaining oily product was then chromatographed on silica gel (eluent: hexane/AcOEt, 1/1), yielding 959 mg (91%) of naphthoquinone **6** as a yellow solid: mp 100–103 °C (EtOH); IR ($CDCl_3$) 3150, 2950, 1665, 1640, 1590, 1580, 1470, 1380, 1335, 1280, 1250, 1242 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 5.99 (s, 1 H), 7.27 (dd, J = 1.5, 8 Hz, 1 H), 7.40–7.57 (m, 5 H), 7.60 (t, J = 8 Hz, 1 H), 7.77 (dd, J = 1.5, 8 Hz, 1 H); MS, m/e 296 (M^+), 187 (M^+ – PhS$^\bullet$).

5-Methoxy-3-(phenylthio)-1,4-naphthoquinone (3b). A solution of 0.152 mL (1.48 mmol) of thiophenol and 84 mg (1.48 mmol) of KOH in 4 mL of MeOH was added dropwise, over 15 min, to a solution of 395 mg (1.48 mmol) of 3-bromo-5-methoxy-1,4-naphthoquinone (**5b**)[11] in 12 mL of THF and 2 mL of MeOH at 0 °C. The resulting suspension was stirred at this temperature for 2 h and then concentrated under reduced pressure. The residue was taken up in 100 mL of CH_2Cl_2 and washed successively with 30 mL of water and 30 mL of brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure and the remaining solid chromatographed on silica gel (eluent: hexane/AcOEt, 1/1), providing 359 mg (82%) of naphthoquinone **3b** as yellow-golden needles: mp 186–187 °C (cyclohexane/EtOH); IR ($CDCl_3$) 3150, 2950, 1650, 1585, 1470, 1380, 1315, 1295, 1275, 1215 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.0 (s, 3 H), 6.01 (s, 1 H), 7.25 (m, 1 H), 7.50 (m, 5 H), 7.57–7.70 (m, 2 H). Anal. Calcd for $C_{17}H_{12}O_3S$: C, 68.90; H, 4.08; S, 10.82. Found: C, 68.58; H, 4.16; S, 10.68.

(1*R,4a*R**,9a*R**)-5-Methoxy-9a-(phenylthio)-1-[(trimethylsilyl)oxy]-1,4,4a,9a-tetrahydro-9,10-anthraquinone (8).** A solution of 379 mg (1.28 mmol) of quinone **6** and 0.71 mL (4.04 mmol) of 1-(trimethylsiloxy)-1,3-butadiene (**7**) in 10 mL of dry CH_2Cl_2 was refluxed for 78 h under nitrogen and then concentrated under reduced pressure. The residue was chromatographed on silica gel (eluent: cyclohexane/AcOEt, 1/1), yielding 442 mg (79%) of the oily adduct **8**: IR ($CDCl_3$) 1708, 1692, 1585, 1468, 1438, 1410, 1392, 1278, 1252 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ –0.24 (s, 9 H), 2.17–2.60 (m, 1 H), 2.90–3.25 (m, 1 H), 3.13 (d, J = 6 Hz, 1 H), 3.85 (s, 3 H), 4.27 (d, J = 4.5 Hz, 1 H), 5.70 (m, 1 H), 6.0 (ddd, J = 2.2, 4.5, 10.5 Hz, 1 H), 7.08–7.33 (m, 4 H), 7.42–7.62 (m, 3 H), 7.73 (dd, J = 1.5, 7 Hz, 1 H).

(4a*R,9a*R**)-5-Methoxy-1-oxo-9a-(phenylthio)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (9).** Jones reagent was added, at 0 °C, to a solution of 200 mg (0.46 mmol) of adduct **8** in 15 mL of acetone, until the disappearance of the starting material was observed (TLC). The excess reagent was destroyed by the adition of *i*-PrOH, and the resulting suspension was filtered on Celite. The filtrate was concentrated under reduced pressure, the remaining solid taken up in CH_2Cl_2, and the solution washed twice with water and then dried over sodium sulfate. The solvent was removed under reduced pressure to yield 151 mg (90%) of the solid enone **9** as a white powder from AcOEt: mp 194–195 °C dec; IR ($CDCl_3$) 3160, 2960, 1705, 1690, 1590, 1470, 1385 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.95 (dddd, J = 2, 4, 5.7, 19.2 Hz, 1 H), 3.06 (dddd, J = 2, 4, 5.9, 19.2 Hz, 1 H), 3.54 (dd, J = 5.7, 5.9 Hz, 1 H), 3.97 (s, 3 H), 6.07 (dt, J = 2, 10.2 Hz, 1 H), 6.99 (dt, J = 4, 10.2 Hz, 1 H), 7.20–7.37 (m, 4 H), 7.52–7.68 (m, 4 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 26.4, 53.8, 56.5, 69.9, 118.2, 120.0, 121.3, 128.4, 128.8, 129.3, 129.7, 135.3, 136.6, 137.0, 147.9, 159.7, 188.9, 190.0, 191.6. Anal. Calcd for $C_{21}H_{16}O_4S$: C, 69.21; H, 4.43; S, 8.80. Found: C, 68.94; H, 4.48; S, 9.08.

1-Hydroxy-5-methoxy-9,10-anthraquinone (10a). A solution of 96 mg (0.26 mmol) of **9** and 53 mg (0.40 mmol) of aluminum

chloride in 10 mL of dry CH_2Cl_2 was stirred at 0 °C for 0.5 h under nitrogen, then hydrolyzed by 20 mL of 4 N HCl, and extracted four times with 50 mL of CH_2Cl_2. The combined organic layers were washed twice with 50 mL of water, dried over magnesium sulfate, and concentrated under reduced pressure. The remaining solid was chromatographed on silica gel (eluent: cyclohexane/AcOEt, 1/1) to yield 60 mg (90%) of anthraquinone **10a** as a yellow solid, mp 183–184 °C (lit.[19] mp 181–183 °C).

1,5-Dimethoxy-9,10-anthraquinone (10b). A suspension of 60 mg (0.25 mmol) of anthraquinone **10a**, 0.35 mL (5.6 mmol) of methyl iodide, and 376 mg (1.6 mmol) of silver oxide in 7 mL of CH_2Cl_2 was stirred in the dark at room temperature for 41 h and then filtered on Celite. The filtrate was concentrated under reduced pressure, giving 63 mg (100%) of anthraquinone **10b**, mp 240–241 °C, which was identified (mixed melting point) with an authentic sample[20] (lit.[20] mp 241–242 °C).

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Registry No. **1a**, 481-39-0; **1b**, 5196-28-1; **2a**, 71700-93-1; **2b**, 71700-92-0; **3a**, 112740-62-2; **3b**, 105245-47-4; **3c**, 112740-63-3; **4b**, 77189-69-6; **5b**, 69833-10-9; **6**, 105259-49-2; **7**, 63383-46-0; **8**, 112740-64-4; **9**, 112740-65-5; **10a**, 52869-21-3; **10b**, 6448-90-4.

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A Novel and Efficient Synthesis of 2(5*H*)-Furanone Derivatives

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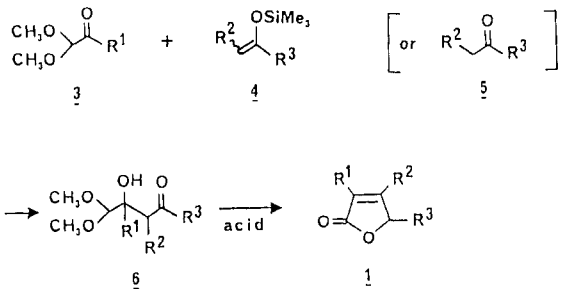
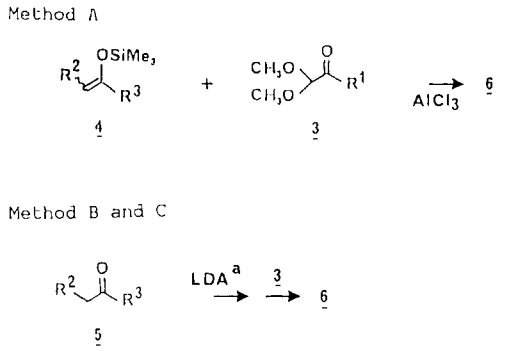
2(5*H*)-Furanones and 5-alkylidene-2(5*H*)-furanones (Δ^2-butenolides) are well-known as basic components of naturally occuring compounds, some of which display a wide range of characteristic physiological properties.[1] In addition, they often serve as useful synthetic intermediates in the stereoselective construction of substituted γ-butyrolactones via conjugate addition or catalytic hydrogenation of the double bond.[2] For example, this approach was used in total syntheses of avenaciolide[3] along with its related compounds[4] and recently has been successfully realized in the stereoselective synthesis of brassinolide.[5] In this work the 5-alkylidene-2(5*H*)-furanone was hydrogenated to the corresponding γ-butyrolactone, providing stereochemical control of four contiguous centers.

Scheme I



Scheme II



[a] 1.1 equiv, R^2 = H, R^3 = CH=C$(CH_3)_2$; 2.2 equiv, R^3 = $CH_2CO_2CH_3$.

Despite the great variety of available synthetic methods,[1,6] scant attention has been paid to practical and efficient synthesis of 3,5-di- or 3,4,5-trisubstituted 2(5*H*)-furanones **1** and 3-alkyl-5-alkylidene-2(5*H*)-furanones **2**.

In this paper, we report a novel and efficient synthesis of 3,5-di- or 3,4,5-trisubstituted 2(5*H*)-furanone analogues **1** in two steps: namely, the cross-aldol condensation of α-keto dimethyl acetal **3** and ketone **5** (or the enol ether equivalent **4**) to lead to the adduct **6**, followed by acid-promoted cyclization of **6** to 2(5*H*)-furanone **1** (as shown in Scheme I).

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