J. CHEM. SOC. PERKIN TRANS. 1 1991

A Short, Convergent Synthesis of Aristolindiquinone [1]

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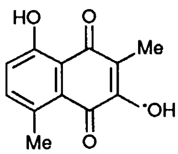
Aristolindiquinone, 2,5-dihydroxy-3,8-dimethyl-1,4-naphthoquinone **1**, is synthesised by the regiochemical addition of 1-methoxy-1-trimethylsiloxypenta-1,3-diene **2** to 5-bromo-2-methoxy-3-methyl-1,4-benzoquinone **3**. The regioisomer 2,8-dihydroxy-3,5-dimethyl-1,4-naphthoquinone **4** is prepared by reaction of the same diene **2** with 2-methoxy-3-methyl-1,4-benzoquinone **11**. The former reaction readily provided sufficient quantities of aristolindiquinone **1** for biological evaluation for fertility regulation in rats, for which purpose it was found to be inactive.

Indian folk medicine makes use of the roots of *Aristolochia indica* (Indian birthwort) as an abortifacient.[2] Recently, the medicinal property of this plant has been verified by the work of Pakrashi,[3] who confirmed its contragestational activity. Further research by Fong and co-workers[4,5] has shown that ethanol extracts of these roots show a marked decrease in the number of pregnancies in rats and hamsters when administered post-coitally. On partition of ethanol extracts a new naphthoquinone, aristolindiquinone **1**, was isolated as a bright orange, crystalline pigment whose structure was initially assigned on the basis of its spectroscopic data,[4] and this was subsequently confirmed both by X-ray diffraction[6] and by synthesis.[7] Owing to its possible biological importance as an antifertility agent, we wished to establish a short, convergent synthesis which would provide gram quantities for biological evaluation.



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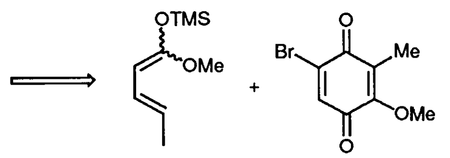
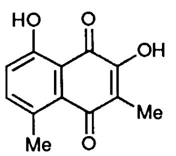


2 **3**



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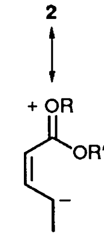

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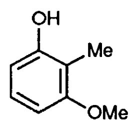
Results and Discussion

A highly convergent route to naphthoquinones involves Diels–Alder reaction between appropriately substituted dienes and benzoquinones. Retrosynthetic analysis of aristolindiquinone **1** implicated the diene **2** and the quinone **3** as the necessary precursors, with the regiochemistry of the forward reaction being controlled by the bromine atom on the quinonoid nucleus.[8,9] The absence of bromine would be predicted to favour the formation of the regioisomer **4** of aristolindiquinone, since it is known[10] that methoxy groups on quinones direct the more negative end of the diene (seen in the alternative resonance contributor **5**) to attack *para* to the methoxy substituent.

Although the bromo quinone **3** is known,[11,12] we believed that a more efficient synthesis could be effected. Accordingly, 3-methoxy-2-methylphenol **6**[13] was smoothly dibrominated to afford the product **7**. This compound was oxidised in very good yield with chromium trioxide in acetic acid to form the desired quinone **3**. The overall yield of the quinone **3** obtained in two steps from the readily available phenol **6** was 81%.

We wished at this stage to investigate the regioselectivity of the addition of an oxygenated diene to the bromo quinone **3**, and therefore used Brasssard's diene, 1,1-dimethoxy-3-trimethylsiloxybuta-1,3-diene **8**,[8a] well known[14] for its reactivity in Diels–Alder reactions, as this compound was then available in our laboratories for use in a separate project.[15,16] Reaction of this diene **8** with the bromo quinone **3** afforded an adduct which was aromatised, without isolation, using aq. sodium hydrogen carbonate. The intermediate naphtholic quinone **9** was not characterised but was immediately methylated with methyl iodide and silver(I) oxide to afford the trimethoxynaphthoquinone **10** in 90% yield in the overall reaction from the bromo quinone **3**.



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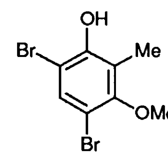

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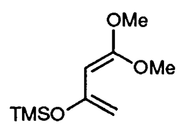

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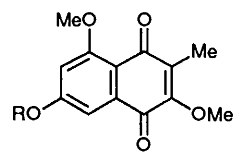

9 R = H
10 R = Me

The importance of bromine in inducing the desired regioselectivity in the Diels–Alder reaction just described was investigated by reaction of the same diene **8** with 2-methoxy-3-methyl-1,4-benzoquinone **11**,[10c,17] the debromo analogue of the bromoquinone **3**. Similar aromatisation followed by methylation afforded the trimethoxynaphthoquinone **12** isomeric with compound **10**. This reaction conclusively showed the importance of bromine in directing regioselectivity in the reaction of dienes with 2-methoxy-3-methyl-1,4-benzoquinone **11**, a fact which has been established previously with a number of other quinones.[8,9]

The diene **2** required for the synthesis of aristolindiquinone **1** was obtained from readily available methyl pent-3-enoate **13**,[18]

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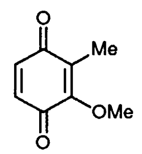
obtained by methylation of the corresponding pent-3-enoic acid.[19] Deprotonation of the ester with lithium diisopropylamide (LDA) followed by quenching with chlorotrimethylsilane afforded the diene in high yield as a mixture of isomers (as shown by ^{1}H NMR spectrometry).



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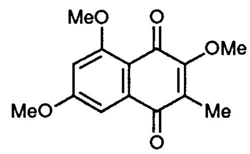

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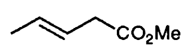

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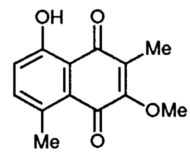

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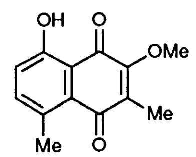

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The Diels–Alder reaction between this new diene **2** and the bromo quinone **3** afforded an adduct, which was pyrolysed at 60–70 °C to yield aristolindiquinone monomethyl ether **14**, as a single product in 60% overall yield from the bromo quinone **3**. Initial efforts to demethylate the methoxy quinone **14** with dil. aq. sodium hydroxide afforded aristolindiquinone **1** in 50% yield. This demethylation was significantly improved upon (85%) by use of boron trichloride.

Alternative reaction of the same diene **2** with 2-methoxy-3-methyl-1,4-benzoquinone **11** afforded the naphthoquinone **15**, isomeric with compound **14**, as the major product together with aristolindiquinone monomethyl ether **14** as the minor product, in the ratio 6:1 as shown by ^{1}H NMR spectrometry. The compounds **14** and **15** were not readily separated by chromatography on account of their similar R_f-values. However, the major product could be obtained pure by successive recrystallisations. Alternatively, on reaction of the mixture of isomers with boron trichloride, only the minor isomer was demethylated (as already described), whereas the major isomer **15** resisted demethylation. This compound could then be readily separated chromatographically from the aristolindiquinone derived from the minor product. This difference in reactivity of the two isomers **14** and **15** to boron trichloride is ascribed to the preferential chelation of the carbonyl *ortho* to the methoxy group in compound **15** with boron attached to the *peri* oxygen, whereas for the precursor **14** to aristolindiquinone, chelation also takes place at the alternative carbonyl, leading to demethylation.

Demethylation of compound **15** was achieved in 38% yield by use of dil. aq. sodium hydroxide, and afforded the compound **4**, isomeric with aristolindiquinone.

Synthetic aristolindiquinone was shown to be identical with a natural sample kindly supplied by Professor Cordell. The m.p. of each sample was identical and the m.p. of their mixture was not depressed. Spectroscopic comparisons and their TLC behaviour showed that the two compounds were identical. However, significant differences in the physical and spectroscopic properties of the isomeric 2,8-dihydroxy-3,5-dimethyl-1,4-naphthoquinone **4** from those of aristolindiquinone **1** were apparent.

The synthesis provides a highly convergent route to aristolindiquinone in 51% overall yield for the two steps from the bromoquinone **3**, and in the four steps from the phenol **6** in 41% yield. Gram quantities of aristolindiquinone were therefore available for biological evaluation, which was carried out by Professor Cordell's group. On examination of the effect of aristolindiquinone on fertility regulation in rats, the compound was found to be inactive.

Experimental

All ^{1}H NMR spectra were measured for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference using either Varian XL-100 or Bruker WH-90 spectrometers; IR spectra were measured for Nujol mulls using a Perkin-Elmer 983 spectrophotometer. Preparative layer chromatography (PLC) was performed on glass plates coated with Merck Kieselgel 60 F_{254}; column chromatography refers to dry-packed columns of the same gel (70–230 mesh). Light petroleum refers to the fraction boiling in the range 60–80 °C, and 'ether' to diethyl ether. The phrase 'residue obtained upon work-up' refers to the material remaining when an organic extract was separated, dried ($MgSO_4$), and evaporated under reduced pressure.

4,6-*Dibromo*-3-*methoxy*-2-*methylphenol* **7**.—The phenol **6** (5.0 g, 36.2 mmol), glacial acetic acid (50 cm^3), and anhydrous sodium acetate (6.5 g, 79.6 mmol) were heated and stirred until dissolution. The solution was cooled to 10 °C and a solution of bromine (11.6 g, 72.4 mmol) in glacial acetic acid (50 cm^3) was added during 10 min. The reaction mixture was stirred for a further 5 min before being thrown into water and repeatedly extracted with methylene dichloride. The organic phase was washed with water and the residue obtained upon work-up crystallised on storage overnight to afford the title product **7** (10.4 g, 98%) as pale yellow needles, m.p. 73 °C (from hexane) (lit.,[12] 74 °C) (Found: C, 32.4; H, 2.7. Calc. for $C_8H_8Br_2O_2$: C, 32.5; H, 2.7%); ν_{max}/cm^{-1} 3407 (OH); δ 2.23 (3 H, s, ArMe), 3.74 (3 H, s, OMe), 5.53 (1 H, s, OH, D_2O-exchangeable) and 7.45 (1 H, s, ArH); *m/z* 298 (M^+, 50%), 296 (M^+, 100), 294 (M^+, 50), 283 (23), 281 (47), 279 (25), 255 (12), 253 (23), 251 (12), 174 (19) and 172 (19).

5-*Bromo*-2-*methoxy*-3-*methyl*-1,4-*benzoquinone* **3**.—The phenol **7** (3.54 g, 11.97 mmol) was dissolved in a mixture of acetic acid (70 cm^3) and water (30 cm^3). A solution of chromium trioxide (3.50 g, 35 mmol) in water (15 cm^3) was added during 10 min with the reaction temperature being maintained below 35 °C. After being stirred for a further 45 min, the reaction mixture was thrown into water and extracted with methylene dichloride. The extract was washed with water and the residue obtained upon work-up was rapidly chromatographed to afford the title product **3** (2.29 g, 83%) as dark yellow needles, m.p. 70–70.5 °C (from propan-2-ol) (lit.,[12] 65 °C) (Found: C, 41.6; H, 3.0. Calc. for $C_8H_7BrO_3$: C, 41.6; H, 3.0%); ν_{max}/cm^{-1} 1654 and 1625 (C=O) and 1590 (C=C); δ 1.99 (3 H, s, Me), 4.02 (3 H, s, OMe) and 7.08 (1 H, s, quinone H); *m/z* 232 and 230 (M^+, each 55%), 231 (17), 229 (12), 202 (30), 200 (30), 189 (15), 187 (15), 133 (20), 131 (19), 123 (20), 121 (13), 93 (69), 83 (57) and 53 (100).

2,5,7-*Trimethoxy*-3-*methyl*-1,4-*naphthoquinone* **10**.—The bromoquinone **3** (100 mg, 0.433 mmol) was dissolved in dry methylene dichloride (8 cm^3) and the reaction system was thoroughly flushed with nitrogen. The diene **8**[8a] (200 mg, 0.989 mmol) was added and the reaction mixture was stirred at room temperature for 24 h, after which aq. sodium hydrogen carbonate (1%; 2 cm^3) was added and the mixture was stirred in air for a further 10 min. This mixture was acidified with dil. hydrochloric acid and the dark brown, oily residue obtained upon work-up was dissolved in chloroform (10 cm^3), to which methyl iodide (709 mg, 5 mmol) and silver(I) oxide (1.09 g, 4.3 mmol) were added, and the mixture was stirred under nitrogen for 18 h, then filtered, the solvent was evaporated off, and the residue was chromatographed (15% ethyl acetate–light petroleum) to afford the *title product* **10** (103 mg, 90%) as yellow needles, m.p. 151–152 °C (from methylene dichloride–propan-2-ol) (Found: C, 64.0; H, 5.3. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%); ν_{max}/cm^{-1} 1664 and 1641 (C=O); δ 2.02 (3 H, s, CMe), 3.89, 3.90 and 3.97 (each 3 H, s, OMe), 6.65 (1 H, d, *J* 2.5 Hz, 6-H), and 7.18 (1 H, d, *J* 2.5 Hz, 8-H); *m/z* 262 (M^+, 100%), 247 (50), 233 (12), 219 (35), 201 (14), 190 (20), 163 (12) and 106 (13).

3,5,7-*Trimethoxy*-2-*methyl*-1,4-*naphthoquinone* **12**.—2-Methoxy-3-methyl-1,4-benzoquinone **11** (66 mg, 0.433 mmol) was substituted for the brominated quinone **3** in the preceding reaction to afford the *title product* **12** (101 mg, 89%), m.p. 141–142 °C (from methylene dichloride–propan-2-ol) (Found: C, 63.7; H, 5.4. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%); ν_{max}/cm^{-1} 1660 (C=O); δ 1.99 (3 H, s, Me), 3.90, 3.93 and 4.06 (each 3 H, s, OMe), 6.64 (1 H, d, *J* 2.5 Hz, 6-H), and 7.21 (1 H, d, *J* 2.5 Hz, 8-H); *m/z* 262 (M^+, 100%), 247 (32), 219 (19), 203 (11), 191 (16) and 169 (11).

1-*Methoxy*-1-*trimethylsiloxypenta*-1,3-*diene* **2**.—Methyl pent-3-enoate **13**[18] was obtained by esterification of pent-3-enoic acid.[19] A solution of dry diisopropylamine (7 cm^3, 53 mmol) in dry tetrahydrofuran (100 cm^3) was cooled to 0 °C under nitrogen, and a solution of butyl lithium in hexane (35 cm^3; 1.6 mol dm^{-3}; 56 mmol) was added. The solution was then cooled to −78 °C, the methyl ester **13** (5.00 g, 43.86 mmol) was added, and the mixture was stirred for 2 min. The derived anion was quenched with chlorotrimethylsilane (9 cm^3, 71 mmol) and the solution was stirred for a further 10 min. The solvent was then removed under reduced pressure (25 mmHg) and the white solid by-product was filtered off, and washed with dry hexane. The hexane was removed under reduced pressure (25 mmHg) to give a pale yellow liquid, which upon distillation gave the pure *title product* **2** (7.9 g, 97%) as an isomeric mixture of liquids, b.p. 81 °C at 1 mmHg, or 41–44 °C at 0.3 mmHg (Found: C, 58.1; H, 9.5. $C_9H_{18}SiO_2$ requires C, 58.0; H, 9.7%); ν_{max}/cm^{-1} 1664 and 1627 (C=C), 1 253 and 1 227 (C–O) and 845 (C–Si); δ 0.21 and 0.24 (9 H, each s, *E*- and *Z*-Me_3Si), 1.69 (3 H, dd, *J* 7.0 and 1.5 Hz, CMe), 3.51 and 3.53 (3 H, each s, *E*- and *Z*-OMe), 4.41 (1 H, m, 2-H) and 5.95–6.33 (2 H, m, 3- and 4-H); *m/z* 186 (M^+, 17%), 89 (14), 82 (100), 75 (10), 73 (32), 59 (11) and 54 (11).

5-*Hydroxy*-2-*methoxy*-3,8-*dimethyl*-1,4-*naphthoquinone* **14**.—The bromoquinone **3** (1.00 g, 4.33 mmol) was dissolved in dry benzene (250 cm^3) and the system was thoroughly flushed with nitrogen. The diene **2** (1.00 g, 5.36 mmol) was then added and the solution was stirred at 60 °C for 4 h. The benzene was removed under reduced pressure and the residue was taken up in a little ether and washed with water. The crude adduct residue obtained upon work-up was heated at 70 °C for 30 min and then chromatographed (eluant 10% ethyl acetate–light petroleum) to give the *title product* **14** (0.60 g, 60%) as orange needles, m.p. 124–125 °C (from hexane) (Found: C, 67.3; H, 5.3. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); ν_{max}/cm^{-1} 1657 and 1624 (C=O); δ 2.02 (3 H, s, 3-Me), 2.58 (3 H, s, 8-Me), 4.07 (3 H, s, OMe), 7.07 (1 H, d, *J* 8.5 Hz, 6-H), 7.32 (1 H, d, *J* 8.5 Hz, 7-H) and 12.80 (1 H, s, OH, D_2O-exchangeable); *m/z* 232 (M^+, 100%), 217 (23) and 189 (30).

2,5-*Dihydroxy*-3,8-*dimethyl*-1,4-*naphthoquinone* (*Aristolindiquinone*) **1**.—Quinone **14** (500 mg, 2.16 mmol) was dissolved in dry methylene dichloride (10 cm^3), a solution of boron trichloride (1.00 g, 8.52 mmol) in methylene dichloride (20 cm^3) was added, and the mixture was stirred at 0 °C for 1 h. The derived dark purple complex was decomposed by the addition of ice–water, and the organic material was extracted with methylene dichloride. The orange residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate–light petroleum) to give aristolindiquinone **1**, (400 mg, 85%) as orange needles, m.p. 191 °C (from MeOH) (lit.,[4] 176–178 °C; lit.,[7] 190 °C) (Found: C, 65.9; H, 4.9. Calc. for $C_{12}H_{10}O_4$: C, 66.0; H, 4.6%); ν_{max}/cm^{-1} 3322 (OH), 1641 and 1615 (C=O); δ 2.03 (3 H, s, 3-Me), 2.62 (3 H, s, 8-Me), 7.12 (1 H, d, *J* 8 Hz, 6-H), 7.32 (1 H, d, *J* 8 Hz, 7-H), 7.62 (1 H, s, 2-OH) and 10.76 (1 H, s, 5-OH); *m/z* 218 (M^+, 100%), 190 (21), 175 (13), 172 (14), 161 (17), 147 (22), 135 (13) and 115 (25).

5-*Hydroxy*-3-*methoxy*-2,8-*dimethyl*-1,4-*naphthoquinone* **15**.—(*a*) 2-Methoxy-3-methyl-1,4-benzoquinone **11** (658 mg, 4.33 mmol) was substituted for the brominated quinone **3** in the above synthesis of the naphthoquinone **14**. Chromatography (eluant 15% ethyl acetate–light petroleum) of the residue obtained after heating afforded a mixture of quinones **15** and **14** (650 mg, 65%) in the ratio 6:1 as shown by ^1H NMR spectrometry. Two recrystallisations from propan-2-ol afforded the *title product* **15** as orange needles, m.p. 144 °C (Found: C, 67.0; H, 5.1. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); ν_{max}/cm^{-1} 1615 (C=O); δ 2.05 (3 H, s, 2-Me), 2.58 (3 H, s, 8-Me), 4.02 (3 H, s, OMe), 7.06 (1 H, d, *J* 8.5 Hz, 7-H), 7.36 (1 H, d, *J* 8.5 Hz, 6-H) and 12.41 (1 H, s, OH, D_2O-exchangeable); *m/z* 232 (M^+, 100%), 217 (29), 202 (17), 189 (48), 187 (14), 161 (12) and 143 (10).

(*b*) As the isomer **14** was difficult to remove by recrystallisation, quinone **15** was also obtained pure as follows. The quinone **11** (900 mg, 5.92 mmol) was treated with the diene **2** (1.36 g, 7.33 mmol) to afford a mixture of isomers **14** and **15** (961 mg, 70%) in the ratio 1:6, respectively. This mixture was dissolved in dry methylene dichloride (20 cm^3) and a solution of boron trichloride (2.7 g, 23.35 mmol) in dry methylene dichloride (55 cm^3) was added, and the mixture was stirred at 0 °C for 30 min. Ice and water were then added and the organic material was extracted with methylene dichloride. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate–light petroleum) whereupon early fractions afforded the product **15** (755 mg, 55%) as orange needles identical with those obtained in (*a*) above. Subsequent fractions yielded aristolindiquinone **1** (103 mg, 8%), indistinguishable from that obtained previously.

2,8-*Dihydroxy*-3,5-*dimethyl*-1,4-*naphthoquinone* **4**.—Compound **15** (500 mg, 2.15 mmol) was added to aq. sodium hydroxide (3%; 300 cm^3) and the mixture was heated to 60 °C and stirred for 30 min. The solution was then acidified with dil. hydrochloric acid and extracted with ether. The residue obtained upon work-up was chromatographed (eluant 20–30% ethyl acetate–light petroleum) to afford first the starting material **15** (79 mg) followed by the *title product* **4** (178 mg, 38%) as orange needles, m.p. 134–136 °C (from MeOH) (Found: C, 65.8; H, 4.7. $C_{12}H_{10}O_4$ requires C, 66.0; H, 4.6%); ν_{max}/cm^{-1} 3443br (OH) and 1616 (C=O); δ 2.08 (3 H, s, 3-Me), 2.63 (3 H, s, 5-Me), 7.08 (1 H, d, *J* 8.5 Hz, 7-H), 7.12 (1 H, s, 2-OH, D_2O-exchangeable), 7.45 (1 H, d, *J* 8.5 Hz, 6-H) and 11.75 (1 H, s, 8-OH, D_2O-exchangeable); *m/z* 218 (M^+, 100%), 190 (13), 173 (11), 172 (12), 147 (10), 115 (10) and 77 (10).

Acknowledgements

Grateful appreciation is expressed to Professor G. A. Cordell, the University of Illinois at Chicago, for a sample of natural aristolindiquinone and to Professors G. A. Cordell, H. H. S. Fong and D. P. Waller, and Ms. A. Martin for the evaluation of our synthetic material in the MB30 test for fertility regulation in rats, for which, at a dose of 30 mg kg^{-1} as a PVP co-precipitate, there was no activity. Dr. C.-T. Che further confirmed the identity of the synthetic and natural materials. Financial support from the South African Council for Scientific and Industrial Research and from the Council of the University of Cape Town is gratefully acknowledged.

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Paper 0/02212H
Received 18*th May* 1990
Accepted 24*th July* 1990