An Approach to (8,3')- and (8,5'·7,3')-Neolignans

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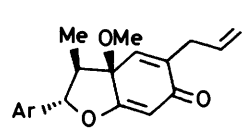
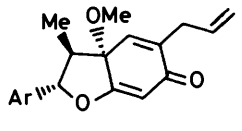
The neolignan analogues (**13**), (**14**), and (**17**) have been prepared by treatment of the corresponding *p*-quinols with methanesulphonyl chloride–triethylamine in the presence of an excess of 1-(3,4-dimethoxyphenyl)propene

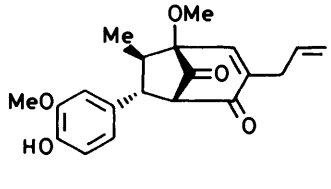
The (8,3')-neolignans[1] comprise a group of natural products which includes denudatins A and B (**1**) and (**2**),[2] mirandins B and A (**3**) and (**4**),[3] and the potent platelet activating factor antagonist kadsurenone (**5**).[4] Related neolignans also include



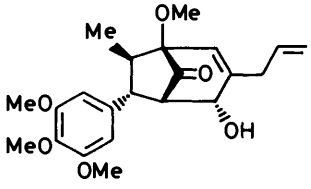


(**1**) Ar = 3,4-methylenedioxyphenyl
(**2**) Ar = 3,4-dimethoxyphenyl
(**3**) Ar = 3,4,5-trimethoxyphenyl
(**4**) Ar = 3,4,5-trimethoxyphenyl
(**5**) Ar = 3,4-dimethoxyphenyl

the (8,5'·7,3')-group represented by liliflodione (**6**)[5] and macrophyllin B (**7**).[6] The total synthesis of these neolignans is of interest because of their biological activity,[7] and the first synthesis of kadsurenone was recently described.[8]



(**6**)

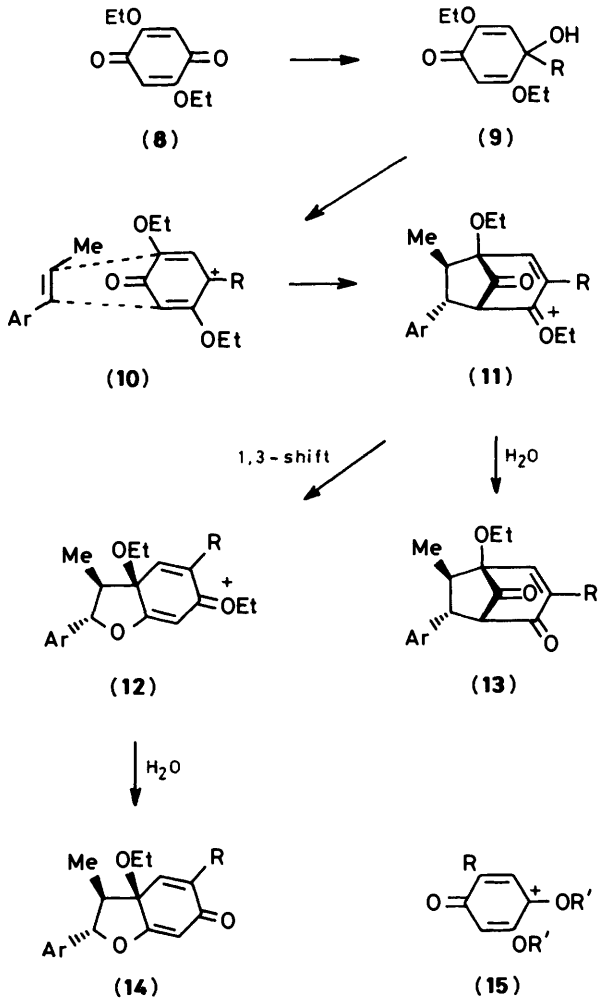


(**7**)

We now report an approach to the synthesis of (8,3')- and (8,5'·7,3')-neolignans as exemplified by the synthesis of the analogues (**13**) and (**14**). This work is based upon the elegant cycloaddition strategy developed for the synthesis of (8,1')- and (8,1'·7,3')-neolignans by Büchi.[9]

Thus the methyl, butyl, and phenyl *p*-quinols (**9a**—**c**) were prepared from 2,5-diethoxy-1,4-benzoquinone (**8**) by mono-protection [Me_3SiCN, KCN, 18-crown-6 (18-c-6)],[10] treatment with the corresponding alkyl- or aryl-lithium, and deprotection. This sequence was found to be easier than direct addition of the alkyl-lithium to the quinone[11] because of the low solubility of the quinone in ethereal solvents. Treatment of the methyl *p*-quinol (**9a**) with methanesulphonyl chloride–triethylamine in the presence of an excess of 1-(3,4-dimethoxyphenyl)propene then gave two products which were separated and identified as the bicyclo[3.2.1]octenedione (**13a**) and the hydrobenzofuran (**14a**); (**13a**):(**14a**) = 75:25, combined yield 53%. These products were identified by comparison of their spectroscopic data with those reported for denudatin B (**2**)[8] and *O*-methyl liliflodione (**19**)[5] (see Table), and the stereochemistry shown was assigned by analogy with the work of Büchi[9] who established that the alkene aryl substituent adopts the *endo* position in cycloadditions of this type. The butyl and phenyl *p*-quinols (**9b,c**) similarly gave adducts (**13b,c**) and (**14b,c**).

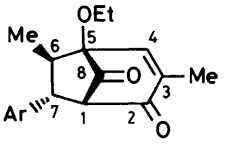
The formation of products (**13**) and (**14**) can be explained in terms of the cycloaddition rearrangement sequence outlined in the Scheme.* Büchi has generated 4,5-dialkoxycyclohexa-



Scheme. **a**, R = Me; **b**, R = Bu; **c**, R = Ph; Ar = 3,4-dimethoxyphenyl

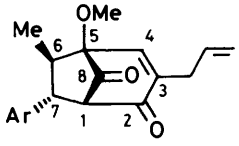
* The detailed mechanisms of these reactions were not investigated. Other possible mechanisms include the formation of the hydrobenzofuran (**14**) by direct addition of cation (**10**) to the alkene to give the intermediate (**12**) without participation of (**11**).

Table. Selected ^{1}H n.m.r. data (δ) of adducts (**13a**), (**14a**), *O*-methyl-liliflodione (**19**), and denudatin B (**2**); Ar = 3,4-dimethoxyphenyl



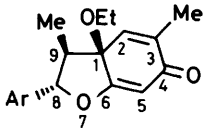
(**13a**)

1.16	(3 H, d, *J* 7 Hz, $CHCH_3$)
2.63	(1 H, m, 6-H)
3.18	(1 H, dd, *J* 6, 7.5 Hz, 7-H)
3.73	(1 H, d, *J* 7 Hz, 1-H)
3.84	(6 H, s, 2 × OCH_3)
6.53	(2 H, m, ArH)
6.76	(1 H, d, *J* 7 Hz, ArH)
7.35	(1 H, narrow m, 4-H)



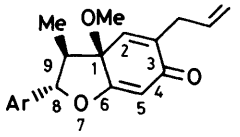
(**19**)[5]

1.18	(3 H, d, *J* 7 Hz, $CHCH_3$)
2.48—2.8	(1 H, m, 6-H)
3.2	(1 H, dd, *J* 5, 7.5 Hz, 7-H)
3.76	(1 H, d, *J* 7.5 Hz, 1-H)
3.84	(6 H, s, 2 × OCH_3)
6.5—6.64	(2 H, m, ArH)
6.78	(1 H, d, *J* 8 Hz, ArH)
7.32	(1 H, br s, 4-H)



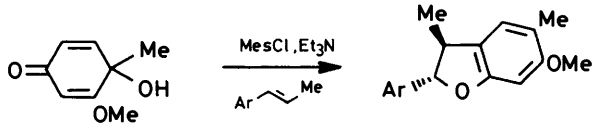
(**14a**)

1.13	(3 H, d, *J* 7 Hz, $CHCH_3$)
2.21	(1 H, m, 9-H)
3.9	(6 H, s, 2 × OCH_3)
5.38	(1 H, d, *J* 10 Hz, 8-H)
5.78	(1 H, s, 5-H)
6.35	(1 H, br s, 2-H)
6.7—6.9	(3 H, m, ArH)

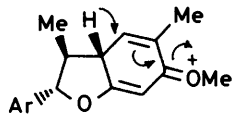


(**2**)[8]

1.15	(3 H, d, *J* 7 Hz, $CHCH_3$)
2.21	(1 H, m, 9-H)
3.92	(6 H, s, 2 × OCH_3)
5.38	(1 H, d, *J* 9.5 Hz, 8-(H)
5.86	(1 H, s, 5-H)
6.30	(1 H, t, *J* 1.5 Hz, 2-H)
6.83—6.92	(3 H, m, ArH)



(**16**) (**17**)



(**18**)

dienone cations (**15**) and trapped them by cycloaddition to electron-rich alkenes.[9] The present work extends this approach to include 4-alkyl substituted cyclohexadienone cations, and shows that these can be generated and trapped without interference from competing dienone–phenol rearrangements.

Finally, the monomethoxy quinol (**16**) was used as a substrate for the cycloaddition. Treatment of this quinol[12] with methanesulphonyl chloride–triethylamine in the presence of an excess of 1-(3,4-dimethoxyphenyl)propene gave a modest yield of the aromatic adduct (**17**). The formation of this product is explained by loss of a proton from the intermediate cation (**18**).

Experimental

I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer, and ^{1}H n.m.r. spectra on a Bruker WH-300 spectrometer using solutions in chloroform and [^{2}H]chloroform, respectively. M.p.s were determined on a Büchi 510 apparatus, and mass spectra were measured on V.G. Micromass 16F and ZAB-1F spectrometers. Flash chromatography used Merck silica 60. All solvents were dried and distilled before use. Ether refers to diethyl ether; light petroleum to the fraction b.p. 40—60 °C.

The potassium cyanide–18-c-6 complex was prepared by dissolving potassium cyanide (0.15 g, 2.3 mmol) and 18-c-6 (0.6 g, 2.3 mmol) in methanol (20 ml). In all reactions requiring this catalyst, the volume of the stock solution containing the required amount of catalyst was added to the reaction vessel and the methanol removed under reduced pressure.

Preparation of p-*Quinols* (**9**).—*2,5-Diethoxy-4-hydroxy-4-methylcyclohexa-2,5-dienone* (**9a**). 2,5-Diethoxy-1,4-benzoquinone (1 g, 5.1 mmol) and anhydrous tetrahydrofuran (THF) (50 ml) were added to KCN–18-c-6 (16 mg, 0.05 mmol), followed dropwise at 0 °C by trimethylsilyl cyanide (0.81 ml, 5.1 mmol). After being stirred for 1 h at 0 °C, the solution was cooled to −78 °C, and methyl-lithium (1.5M solution in ether; 4 ml, 6.12 mmol) was added, and the mixture stirred at −78 °C for 4 h before being allowed to warm to room temperature and quenched (excess of saturated aqueous NH_4Cl). The mixture was extracted with ether and the extract concentrated under reduced pressure to give a dark orange solid which was purified by flash chromatography using light petroleum–ethyl acetate (4:1) as eluant to give 1-cyano-2,5-diethoxy-4-hydroxy-4-methyl-1-trimethylsilyloxycyclohexa-2,5-diene (0.66 g, 41%). To this dissolved in anhydrous THF (25 ml) was added at 0 °C an anhydrous 1M solution of tetrabutylammonium fluoride in THF (2.5 ml, 2.5 mmol). After 2 h, the mixture was extracted with dichloromethane, and the extract concentrated under reduced pressure; flash chromatography of the residue using light petroleum–ethyl acetate (1:2) as eluant gave the *title compound* (**9a**) (0.29 g, 65%) as a crystalline solid, m.p. 119—121 °C (from ether) (Found: C, 62.3; H, 7.7. $C_{11}H_{16}O_4$ requires

C, 62.25; H, 7.6%); $\nu_{max.}$ 3 600, 3 300, 1 675, 1 650, and 1 610 cm^{-1}; δ_H 1.40 and 1.42 (each 3 H, t, *J* 7 Hz, CH_2CH_3), 1.53 (3 H, s, CH_3), 2.65 (1 H, br s, OH), 3.82 (2 H, m, CH_2CH_3), 3.98 (2 H, q, *J* 7 Hz, CH_2CH_3), and 5.45 and 5.53 (each 1 H, s, vinylic H); *m/z* 212 (M^+, 5%), 197 ($M^+ - 15$, 50%), 195 ($M^+ - 17$, 45%), 169 ($M^+ - 43$, 35%), and 141 ($M^+ - 71$, 100%).

The butyl *p*-quinol (**9b**) was similarly prepared from 2,5-diethoxy-1,4-benzoquinone using butyl-lithium. Recrystallisation from ether gave 4-*butyl*-2,5-*diethoxy*-4-*hydroxycyclohexa*-2,5-*dienone* (**9b**), as white needles, m.p. 97—99 °C (Found: C, 66.2; H, 8.85. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.7%); $\nu_{max.}$ 3 600, 3 430, 1 670, 1 650, and 1 610 cm^{-1}; δ_H 0.85 (3 H, t, *J* 7 Hz, CH_3), 1.0 and 1.17 (each 1 H, m, *H*CH), 1.25 (2 H, m, CH_2), 1.42 and 1.43 (each 3 H, t, *J* 7 Hz, CH_3), 1.75 and 1.94 (each 1 H, m, HC*H*), 2.4 (1 H, br s, OH), 3.85 (2 H, q, *J* 7.5 Hz, OCH_2CH_3), 3.98 (2 H. m, OCH_2CH_3), and 5.45 and 5.52 (each 1 H, s, vinylic H); *m/z* 254 (M^+, 5%), 197 ($M^+ - 57$, 75%), 169 ($M^+ - 85$, 60%), and 141 ($M^+ - 113$, 100%).

The phenyl *p*-quinol (**9c**) was similarly prepared from 2,5-diethoxy-1.4-benzoquinone using phenyl-lithium. Recrystallisation from ether gave 2,5-*diethoxy*-4-*hydroxy*-4-*phenylcyclohexa*-2,5-*dienone* (**9c**), as white needles, m.p. 125—127 °C (Found: C. 69.9; H, 6.65. $C_{16}H_{18}O_4$ requires C, 70.1; H, 6.6%); $\nu_{max.}$ 3 700, 3 570, 1 670, 1 650, and 1 615 cm^{-1}; δ_H 1.28 and 1.38 (each 3 H. t. *J* 7.5 Hz, CH_2CH_3), 3.22 (1 H, br s, OH), 3.77 and 3.97 (each 2 H, m, CH_2CH_3), 5.53 and 5.67 (each 1 H, s, vinylic H), and 7.25—7.45 (5 H, m, ArH); *m/z* 274 (M^+, 15%), 245 ($M^+ - 29$. 92%), and 105 ($M^+ - 169$, 100%).

Cycloadditions.—Methanesulphonyl chloride (22 μl, 0.29 mmol) was added to a cooled solution (0 °C) of the methyl *p*-quinol (**9a**) (50 mg, 0.24 mmol) in dichloromethane (0.5 ml) containing triethylamine (0.36 mmol) and 1-(3,4-dimethoxyphenyl)propene (0.2 ml, 1.2 mmol), and the mixture stirred for 5 h at 0 °C and then at room temperature for 17 h; it was then quenched by addition of water. The products were extracted into dichloromethane, and the extracts washed with aqueous Na_2CO_3, water, and brine, before being dried ($MgSO_4$), and concentrated under reduced pressure to leave an oil. Flash chromatography using light petroleum–ethyl acetate as eluant gave first 8-(3,4-*dimethoxyphenyl*)-1-*ethoxy*-3,9-*dimethyl*-7-*oxabicyclo*[4.3.0]*nona*-2,5-*dien*-4-*one* (**14a**) (12 mg, 15%); $\nu_{max.}$ 1 745, 1 675, 1 650, and 1 635 cm^{-1}; δ_H 1.13 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.15 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.0 (3 H, d, *J* 0.5 Hz, CCH_3), 2.16 (1 H, m, 9-H), 3.3 (2 H, q, *J* 7.5 Hz, OCH_2CH_3), 3.9 (6 H, s, 2 × OCH_3), 5.38 (1 H, d, *J* 10 Hz, 8-H), 5.78 (1 H, s, 5-H), 6.35 (1 H, br s, 2-H), and 6.7—6.9 (3 H, m, ArH); *m/z* 344 (M^+, 100%). Secondly, 7-(3,4-*dimethoxyphenyl*)-5-*ethoxy*-3,6-*dimethylbicyclo*[3.2.1]*oct*-3-*ene*-2,8-*dione* (**13a**) (33 mg, 41%) was eluted. m.p. 90—92 °C (from ethyl acetate) (Found: C, 69.9; H, 7.25. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.0%); $\nu_{max.}$ 1 775 and 1 690 cm^{-1}; δ_H 1.16 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.33 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.82 (3 H, d, *J* 0.5 Hz, CCH_3), 2.63 (1 H, m, 6-H), 3.18 (1 H, dd, *J* 6, 7.5 Hz, 7-H), 3.72 (1 H, m, HC*H*), 3.73 (1 H, d, *J* 7 Hz, 1-H), 3.84 (6 H, s, 2 × OCH_3), 4.12 (1 H, m, *H*CH), 6.53 (2 H, m, ArH), 6.76 (1 H, d, *J* 7 Hz, ArH), and 7.35 (1 H, narrow m, 4-H); *m/z* 344 (M^+, 45%) and 178 ($M^+ - 166$, 100%).

Similar treatment of the butyl and phenyl *p*-quinols (**9b,c**) gave mixtures of the corresponding adducts (**13**) and (**14**) (35—40%), identified by spectroscopic comparison with (**13a**) and (**14a**); (**13b**):(**14b**) = 5:1; (**13c**):(**14c**) = 3:1 (^1H n.m.r.). Repeated chromatography of these mixtures gave samples of the major adducts. 3-*Butyl*-7-(3,4-*dimethoxyphenyl*)-5-*ethoxy*-6-*methylbicyclo*[3.2.1]*oct*-3-*ene*-2,8-*dione* (**13b**) so obtained was an oil, $\nu_{max.}$ 1 770, 1 680, and 1 520 cm^{-1}; δ_H 0.93 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.23 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.2—1.6 (4 H, m, CH_2CH_2), 1.39 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.2 (2 H, m, CH_2), 2.68 (1 H, m, 6-H), 3.25 (1 H, dd, *J* 5, 7.5 Hz, 7-H), 3.75 (1 H, m, HC*H*), 3.8 (1 H, d, *J* 7.5 Hz, 1-H), 3.92 (6 H, s, 2 × OCH_3), 4.15 (1 H, m, *H*CH), 6.5—6.9 (3 H, m, ArH), and 6.93 (1 H, br s, 4-H); *m/z* 386 (M^+, 40%), 191 ($M^+ - 195$, 80%), and 178 ($M^+ - 208$, 100%). 7-(3,4-*Dimethoxyphenyl*)-5-*ethoxy*-6-*methyl*-3-*phenylbicyclo*[3.2.1]*oct*-3-*ene*-2,8-*dione* (**13c**) had $\nu_{max.}$ 1 767, 1 714, 1 685, and 1 520 cm^{-1}; δ_H 1.23 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.38 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.82 (1 H, m, 6-H), 3.32 (1 H, dd, *J* 5, 7 Hz, 7-H), 3.72 and 3.85 (each 3 H, s, OCH_3), 3.82 (1 H, m, HC*H*), 3.89 (1 H, d, *J* 7 Hz, 1-H), 4.21 (1 H, m, *H*CH), 6.6—6.8 (3 H, m, ArH), 7.15—7.4 (5 H, m, ArH), and 7.68 (1 H, s, 4-H); *m/z* 407 ($M^+ + 1$).

Following a similar procedure the monomethoxy *p*-quinol (**16**) (232 mg, 1.5 mmol) gave a single product after flash chromatography (light petroleum–ethyl acetate, 10:1 as eluant) identified as 2-(3,4-*dimethoxyphenyl*)-6-*methoxy*-3,5-*dimethyl*-2,3-*dihydrobenzo*[b]*furan* (**17**) (70 mg, 15%), m.p. 137—139 °C (from ether–hexane) (Found: C, 72.4; H, 7.15. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%); $\nu_{max.}$ 1 620, 1 600, 1 262, 1 160, 1 140, and 1 027 cm^{-1}; δ_H 1.38 (3 H, d, *J* 7 Hz, $CHCH_3$), 2.19 (3 H, s, Ar-CH_3), 3.4 (1 H, m, 3-H), 3.83, 3.88, and 3.89 (each 3 H, s, OCH_3), 5.07 (1 H, d, *J* 8 Hz, 2-H), 6.48 (1 H, s, ArH), and 6.8—7.0 (4 H, m, ArH); *m/z* 314 (M^+, 100%).

Acknowledgements

We thank the S.E.R.C. for support (for S. V. M.), Dr. A. E. Derome and Mrs. McGuinness for ^1H n.m.r. spectra, Dr. R. T. Aplin for mass spectra, and Dr. G. Kneen for drawing our attention to this problem.

References

1 D. A. Whiting, *Nat. Prod. Rep.*, 1985, **2**, 191.
2 J. Iida, K. Ichino, and K. Ito, *Phytochemistry*, 1982, **21**, 2939.
3 C. J. Aiba, O. R. Gottlieb, F. M. Pagliosa, M. Yoshida, and M. T. Magalhaes, *Phytochemistry*, 1977, **16**, 745.
4 T. Y. Shen, S.-B. Hwang, M. N. Chang, T. W. Doebber, M.-H. T. Lam, J. S. Wu, X. Wang, C. Q. Han, and R. Z. Li, *Proc. Natl. Acad. Sci., U.S.A.*, 1985, **82**, 672.
5 J. Iida and K. Ito, *Phytochemistry*, 1983, **22**, 763.
6 R. B. Filho, R. Figlinolo, and O. R. Gottlieb, *Phytochemistry*, 1980, **19**, 659.
7 R. S. Ward, *Chem. Soc. Rev.*, 1982, **11**, 75.
8 M. M. Ponpipom, B. Z. Yue, R. L. Bugianesi, D. R. Brooker, M. N. Chang, and T. Y. Shen, *Tetrahedron Lett.*, 1986, **27**, 309.
9 G. Büchi and C.-P. Mak, *J. Am. Chem. Soc.*, 1977, **99**, 8073; G. Büchi and P.-S. Chu, *J. Org. Chem.*, 1978, **43**, 3717; G. Büchi and P.-S. Chu, *J. Am. Chem. Soc.*, 1981, **103**, 2718.
10 A. J. Guildford and R. W. Turner, *Synthesis*, 1982, 46.
11 A. Fischer and G. N. Henderson, *Tetrahedron Lett.*, 1980, **21**, 701.
12 D. Liotta, M. Saindane, and C. Barnum, *J. Org. Chem.*, 1981, **46**, 3369.

Received 21*st January* 1988; *Paper* 8/00237A