

## Regioselective Suprafacial 1,5-Hydrogen Shifts in *o*-Quinodimethanes; a Route to 4-Deoxypodophyllotoxin

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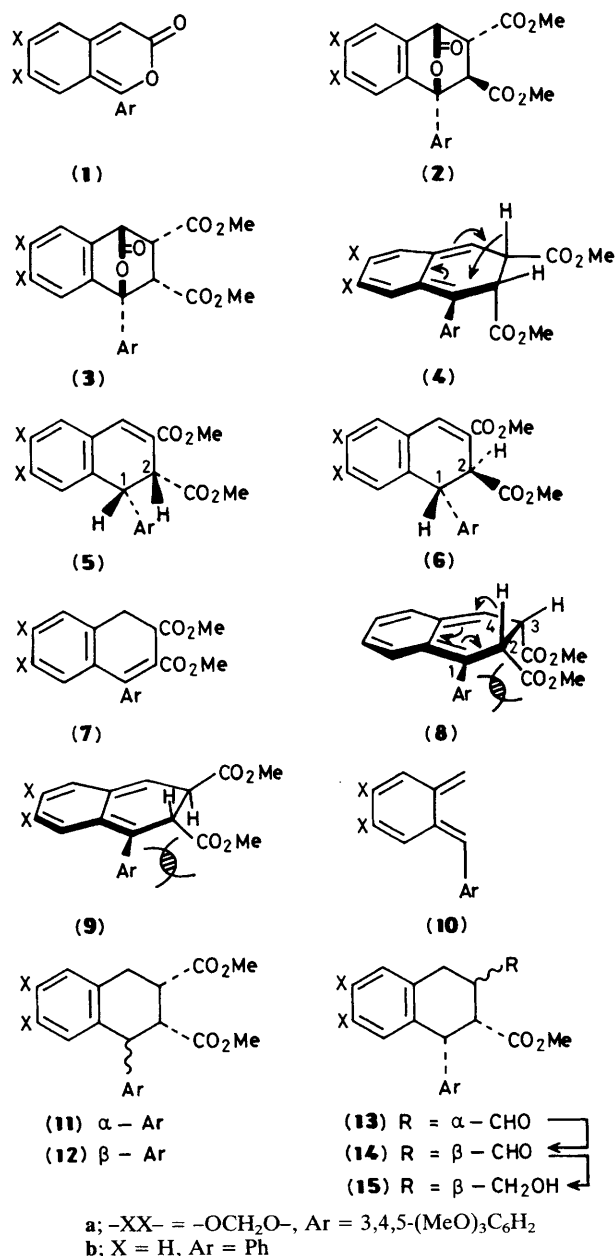
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The *o*-quinodimethane intermediate (**4a**) with *cis*-CO<sub>2</sub>Me groups undergoes regioselective 1,5-hydrogen shift to the *cis*-dihydronaphthalene (**5a**) whilst its *trans*-isomer (**9a**) gives both 1,5-hydrogen shift products (**6a**) and (**7a**); (**5a**) is readily converted into 4-deoxypodophyllotoxin.

We recently described the synthesis of podophyllotoxin and epipodophyllotoxin from the stable 2-benzopyran-3-one (**1a**) via its dimethyl fumarate adduct (**2a**).<sup>1</sup> Attempts to prepare the related *endo*-dimethyl maleate adduct (**3a**) have now revealed an easy thermal decarboxylation of (**3a**) leading to the *o*-quinodimethane (**4a**) which undergoes a suprafacial and highly regioselective 1,5-hydrogen shift to the *cis*-dihydro-

naphthalene (**5a**). This new route to *cis*-dihydronaphthalenes is used to clarify contradictory reports on the stereochemistry of the addition of dimethyl maleate to  $\alpha$ -aryl-*o*-quinodimethanes,<sup>2,3</sup> and to provide a simple route to 4-deoxypodophyllotoxin.

The pyrone (**1a**) and dimethyl maleate (1.2 equiv.) in boiling xylene (3.5 h, Ar) gave the dihydronaphthalene (**5a**)



(71%), m.p. 130–132°C. The *cis*-stereochemistry of (5a) follows from the coupling constant (8.0 Hz) between the C-1 and C-2 protons. With 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in boiling benzene (5a) was cleanly converted into the *trans*-isomer (6a), m.p. 155–158°C, in which the coupling between the C-1 and C-2 protons is reduced to 3.0 Hz. These observations agree with literature data for related *cis*–*trans*-isomers.<sup>4</sup> The formation of (5a) requires easier decarboxylation of the putative intermediate adduct (3a) than that for the *endo*-adduct (3b) which is isolated by trapping the unstable pyrone (1b) in boiling acetic anhydride.<sup>5</sup> There is some evidence<sup>6</sup> that oxygen substituents speed the decarboxylation of isochroman-3-ones. Heating (3b) in diphenyl ether in base-washed glassware at 183°C (45 min) gave the *cis*-dihydronaphthalene (5b) (88%),<sup>†</sup>  $J_{1,2}$  8.5 Hz, which was

<sup>†</sup> A reaction conducted in  $C_6D_6$  in a sealed n.m.r. tube and monitored by 400 MHz  $^1H$  n.m.r. spectroscopy failed to reveal any other product.

cleanly isomerised by DBN to the *trans*-isomer (6b),  $J_{1,2}$  3.0 Hz.

The furmarate adducts (2a) and (2b) required heating at 170°C (115 min) and 220°C (360 min) respectively for decarboxylation. In neither case was the 1,5-hydrogen shift regioselective; (2a) gave (6a) and (7a) (ratio 1:1.5) and (2b) gave (6b) and (7b) (ratio 2:1). The corresponding *cis*-dihydronaphthalenes (5a) and (5b) were absent from these thermolyses (400 MHz n.m.r. spectra) indicating suprafacial hydrogen shifts. The regioselectivity of the 1,5-hydrogen shift in the *cis*-*o*-quinodimethanes (4; arrows) is probably steric in origin. The transition state (TS) for the observed hydrogen migration from C-3 to C-1 is related to the ground-state conformation shown in (4) whilst the TS for the disfavoured shift from C-2 to C-4 is related to the ground-state conformation (8) which is destabilised by near eclipsing of the aryl and methoxycarbonyl groups. For the *trans*-*o*-quinodimethane the TSs for both possible 1,5-shifts are related to the same destabilised ground state conformer (9). Consequently there is little preference for either shift, and both occur.

Whilst addition of dimethyl maleate to (10a) is said to give the *endo*-adduct (11a),<sup>3</sup> addition of the same dienophile to (10b) is reported to give the *exo*-adduct (12b).<sup>2</sup> Catalytic reduction of (5a) and (5b) ( $H_2/Pd-C/EtOAc$ , 20°C, 16 h) resulted in each case in one major product formed by delivery of hydrogen to the less hindered  $\beta$ -face of the molecule. Our products (11a) and (11b) are clearly different from those reported<sup>2,3</sup> as would be expected if dimethyl maleate prefers *exo*-addition to both (10a) and (10b).<sup>‡</sup>

The readily available dihydronaphthalene (5a) is an attractive intermediate for lignan synthesis. Thus (5a) is readily converted into 4-deoxypodophyllotoxin. Selective reduction of the C-3 methoxycarbonyl group ( $LiEt_3BH$ , –70°C), reduction of the olefinic double bond in the resulting allylic alcohol ( $H_2/Rh-Al_2O_3$ , 20°C,  $C_6H_6$ , 22 h), and Swern oxidation gave the aldehyde (13a). This was selectively epimerised at C-3 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF) (25°C, 24 h) to give (14a) (93%). Catalytic reduction ( $H_2/Pd-C$ ) then gave (15a) which was readily lactonised to 4-deoxypodophyllotoxin (35 min, 66°C, 80%) using our  $ZnCl_2$ -THF-4 Å molecular sieves procedure.<sup>1</sup>

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## References

- D. W. Jones and A. M. Thompson, *J. Chem. Soc., Chem. Commun.*, 1987, 1797.
- J. L. Charlton and T. Durst, *Tetrahedron Lett.*, 1984, **25**, 5287; F. C. Koyuna and J. L. Charlton, *J. Org. Chem.*, 1985, **50**, 4829.
- J. Mann and S. E. Piper, *J. Chem. Soc., Chem. Commun.*, 1982, 431; J. Mann, S. E. Piper, and L. K. P. Yeung, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2081.
- M. Pfau, S. Combrisson, J. E. Rowe, and N. D. Heindel, *Tetrahedron*, 1978, **34**, 3459.
- D. W. Jones and R. L. Wife, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1654.
- R. J. Spangler, B. J. Beckmann, and J. H. Kim, *J. Org. Chem.*, 1977, **42**, 2989.

<sup>‡</sup> Added in proof. Unlike the addition of dimethyl maleate to (10a) the corresponding addition of the more compact maleic anhydride is *endo*-selective (S. Takano, S. Otaki, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1985, 485, and ref. 3). This agrees with a steric explanation for *exo*-selectivity in additions to certain  $\alpha,\alpha'$ -diphenyl substituted *o*-quinodimethanes (see ref. 5 and C. W. G. Fishwick and D. W. Jones, in 'The Chemistry of Quinoid Compounds', vol. II, ed. S. Patie and Z. Rappoport, Wiley, London, 1988, p. 403).