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

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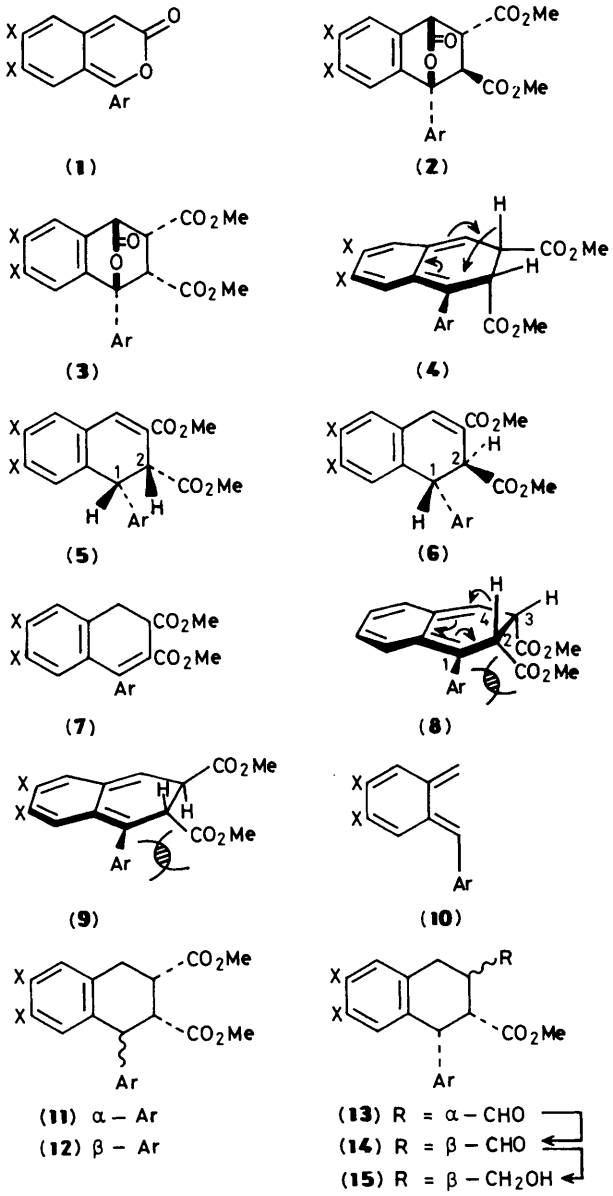
The *o*-quinodimethane intermediate (**4a**) with *cis*-CO_2Me groups undergoes regioselective 1,5-hydrogen shift to the *cis*-dihydronaphthalene (**5a**) whilst its *trans*-isomer (**9a**) gives both 1,5-hydrogen shift products (**6a**) and (**7a**); (**5a**) is readily converted into 4-deoxypodophyllotoxin.

We recently described the synthesis of podophyllotoxin and epipodophyllotoxin from the stable 2-benzopyran-3-one (**1a**) *via* its dimethyl fumarate adduct (**2a**).[1] 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*-dihydronaphthalene (**5a**). This new route to *cis*-dihydronaphthalenes is used to clarify contradictory reports on the stereochemistry of the addition of dimethyl maleate to α-aryl-*o*-quinodimethanes,[2,3] 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**)



a; -XX- = $-OCH_2O-$, Ar = $3,4,5\text{-}(MeO)_3C_6H_2$
b; X = H, Ar = Ph

(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.[4] 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.[5] There is some evidence[6] 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%),† $J_{1,2}$ 8.5 Hz, which was 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**),[3] addition of the same dienophile to (**10b**) is reported to give the *exo*-adduct (**12b**).[2] 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 β-face of the molecule. Our products (**11a**) and (**11b**) are clearly different from those reported[2,3] as would be expected if dimethyl maleate prefers *exo*-addition to both (**10a**) and (**10b**).‡

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.[1]

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† 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.

‡ *Added in proof.* Unlike the addition of dimethyl maleate to (**10a**) the corresponding addition of the more compact maleic unhydride 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 α,α′-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. Patcie and Z. Rappoport, Wiley, London, 1988, p. 403).