Intramolecular Diels–Alder Additions to 2-Benzopyran-3-ones; *Anti*-selectivity induced by the Phenylsulfonyl Group

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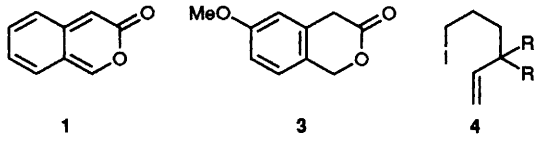
The 2-benzopyran-3-ones **7a** and **7c** undergo intramolecular Diels–Alder addition *via* preferred *endo*-addition of the connecting chain, whereas for **7d** and **7e** (X = SO_2Ph), *exo*-addition of the chain is preferred; the main adducts from the latter additions (**9d** and **9e**), give the diterpene-related products **12** (R = H, Y = OMe) and **12** (R = Me, Y = OMe) upon treatment with sodium amalgam.

Intermolecular Diels–Alder additions of derivatives of 2-benzopyran-3-one **1** are useful in the synthesis of A ring aromatic steroids,[1a] lignans[1b] and anthracylinones,[1c] but the intramolecular additions (IMDA additions) have not been explored. Such additions appeared to be appropriate for the synthesis of diterpenoids such as carnosol,[2] pisiferic acid[3] and taxodione[4] (Scheme 1). The majority of *o*-quinodimethanes undergo *exo*-selective IMDA addition of the connecting chain when the addend is a simple vinyl group and the chain consists of three or four methylene groups. Accordingly, **2** might be expected to give the carnosol stereochemistry (Scheme 1).[5]

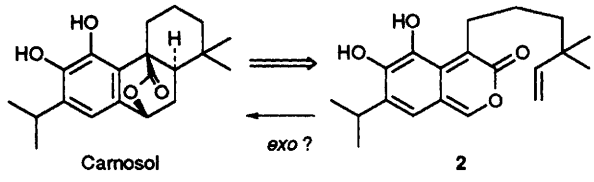
The model compounds required to test this idea were prepared starting with alkylation of the readily available isochroman-3-ones *e.g.* **3**[6] with the iodides **4** (R = H or Me) [$KN(SiMe_3)_2$, 20 h, 20 °C]. The alkylated products **5a** and **5c** were readily converted into the *o*-formylphenylacetic acids **6a** and **6c** (Scheme 2). Upon heating in boiling acetic anhydride, the acids produced strong yellow colours consistent with generation of the pyrones **7**. On continued heating, the yellow colours faded and isolation gave the adducts **8a** and **9a** from **6a**, and **8c** and **9c** from **6c** in the ratios given in Table 1.† The predominant *exo*-chain addition observed for **10**[7] suggests that the lactone moiety, CO.O in the pyrones results in a greater steric barrier to *exo* than *endo* addition.‡ In seeking to reverse the *endo*-selectivity observed for pyrones **7a** and **7c** we noted the work of Craig *et al.*[8] who observed increased *endo*-chain addition in the decatrienes **11**[9] upon introducing an *E*-SO_2Ph group (Scheme 3). The effect was rationalised in terms of the bulk of the SO_2Ph group and greater steric hindrance in the *endo*-SO_2Ph (*exo*-chain) transition state. Greater steric congestion for *exo*-than *endo*-addition in the case of pyrone systems of type **2** suggested that a bulky *E*-SO_2Ph group would favour the *endo*-position, forcing the connecting chain to go *exo*.

Ozonolysis of **5b** and **5c** gave the corresponding aldehydes which, upon addition of $PhSO_2CH_2Li$ (THF, −78 °C, 1 h) and dehydration of the resulting hydroxysulfones ($MeSO_2Cl$, Et_3N, THF, −5 °C, 30 min) gave **5d** and **5e**. These compounds were then treated as in Scheme 2 to give **6d** and **6e**. Dehydration of the sulfones proceeded smoothly to give the adduct pairs **8d/9d** and **8e/9e** respectively. As shown in Table 1, the desired change of addition stereochemistry is indeed observed, and in agreement with a steric effect it is more successful when R = H than when R = Me. Having served its purpose, the phenylsulfonyl group can be removed from **9d** and **9e** by treatment with sodium amalgam, when reductive β-elimination with the lactone provides carboxylic acids **12** (R = H, Y = OMe) and **12** (R = Me, Y = OMe). The latter acid was different to the *cis*-isomer **13** (R = Me, Y = OMe) produced from **8c** (Scheme 2). The addition stereochemistry is diverted more effectively by the SO_2Ph group in **7d** than by the CO_2Me group in **7f**, in better agreement with a steric rather than a secondary MO–MO interaction effect.



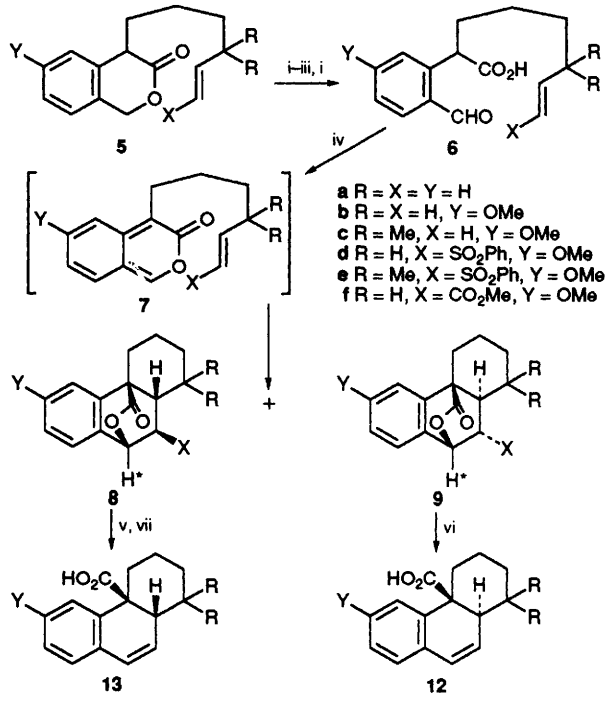
1 3 4

In conclusion, we have shown that IMDA additions to 2-benzopyran-3-ones allow preparation of either *cis*- or *trans*-fused hydrophenanthrenes related to natural diterpenoids.§ The use of the phenylsulfonyl group to gain access to the *trans*-fused system complements the work of Craig *et al.*, in



Carnosol 2

Scheme 1

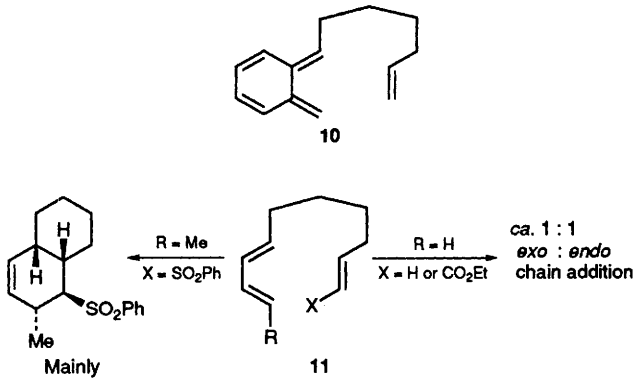


Scheme 2 *Reagents and conditions*: i, Na_2CO_2–H_2O–MeOH, reflux, 1 h; ii, CH_2N_2–Et_2O, 0 °C; iii, Swern oxidation; iv, Ac_2O, 140 °C; v, MeOH–HCl (g), reflux; vi, 5% Na/Hg–THF–MeOH–Na_2HPO_4, 0 °C, 16 h; vii, $KOBu^t$, Bu^tOH, reflux

Table 1

Pyrone	Adduct ratio[a] **8**:**9**
7a	4.5:1.0
7c	6.0:1.0
7d	1.0:4.2
7e	1.0:2.6
7f	1.0:3.4

[a] Yield of **8** and **9** >80% in all cases.



Scheme 3

which the same group is used to favour *cis*-fused adducts.[8] Our results may extend to other dienes linked between their termini. Such systems include important Diels–Alder dienes like cyclopentadienes, cyclohexadienes, furans, simple pyrones, and other *o*-quinodimethanes. We also suggest that any diene with a *Z*-substituent will show an increased tendency to *endo*-addition of the *larger* group of a *trans* dienophile in both inter- and intra-molecular addition. Indeed, *o*-quinodimethanes with a *Z*-cyano group break the general rule of *exo*-chain preference in IMDA additons to *o*-quinonoid dienes.[10]

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Footnotes

† The stereochemistry of the adducts follows from their high field ^{1}H NMR spectra. In particular, **8c** and **9c** are distinguished by the presence of a high field methyl resonance for **8c** (δ 0.17), which is absent for **9c**. Similarly, **8a** shows a strongly shielded methylene proton (δ 0.68), not shown by **9a**. In addition to these features the sulfone adducts exhibit H* (see **8** and **9**, Scheme 2) as a singlet ($w_{1/2}$ *ca.* 1 Hz) for **8e** and as a well-defined doublet (*J* 3.5 Hz) for **9e**.[11]

‡ Strong *endo*-selectivity in the addition of cyclopentene to **1** can be attributed in part to steric repulsion involving the lactone CO.O group. Some other factor favouring *endo*-addition is suggested by the *endo*-preference observed for addition of *E*-α-cyano- and *E*-α-methoxycarbonyl-*o*-quinodimethane to cyclopentene. This other factor may be a secondary MO–MO interaction.[11]

§ Whilst the current route involving desulfonylation together with lactone cleavage is ideally suited for pisiferic acid[3] synthesis, the lactone required for carnosol (Scheme 1) should also be available from products of type **12** *via* bromolactonisation (Me_2SO, H_2O, NBS) followed by debromination (Bu_3SnH). We have already shown that a related strategy converts **13** (R = Me, Y = OMe) into **8** (R = Me, Y = OMe, X = H).

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