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# Synthesis of Pisiferol Revisited; Control of Stereochemistry in an Intramolecular Diels-Alder Reaction

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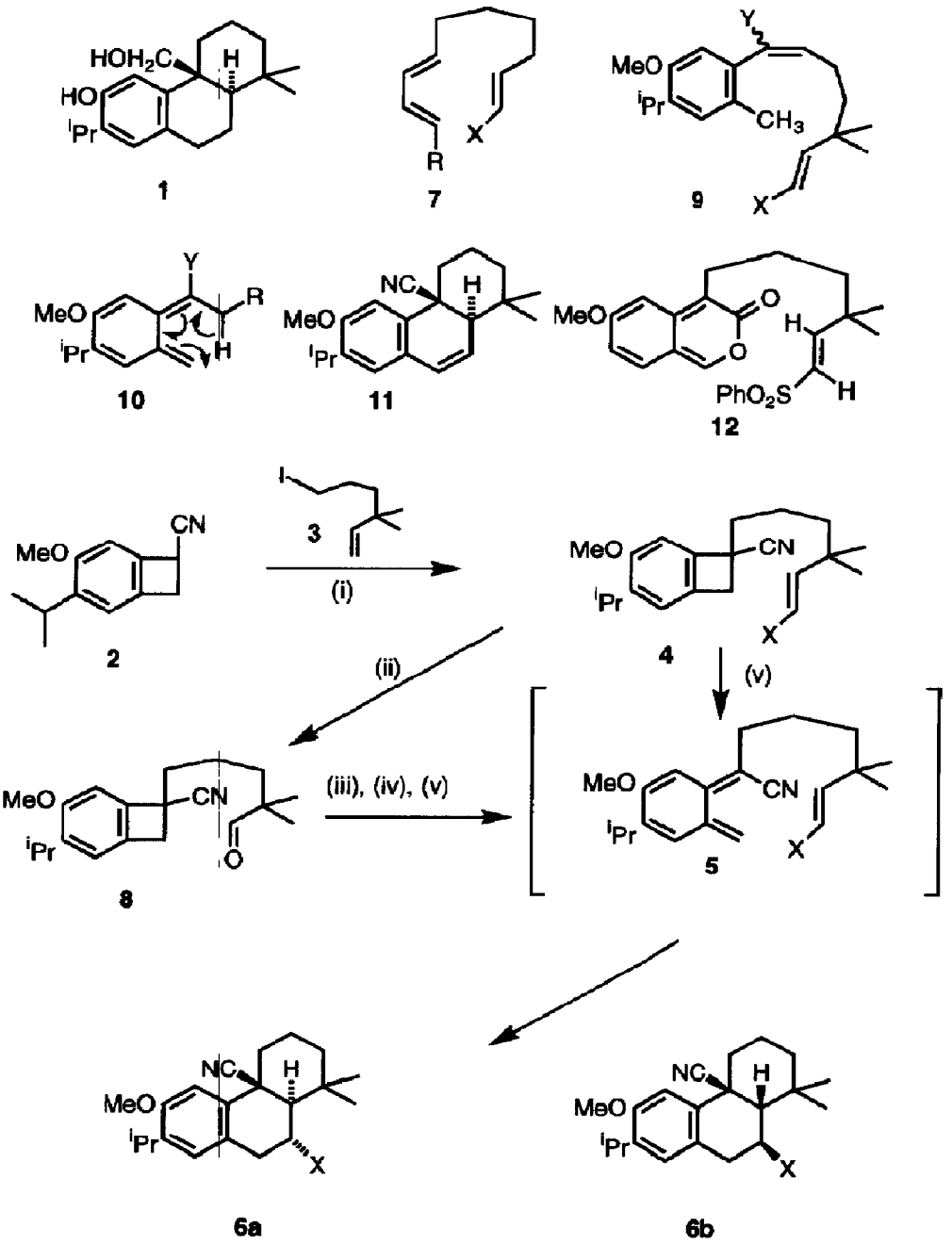
**Abstract:** Thermolysis of 4(X=H) gives **6a** and **6b**(X=H) in a ratio of 1:4 whereas **4** (X=$SO_2Ph$) gives more of the *trans*-ring junction product **6a**(X=$SO_2Ph$) suitable for the synthesis of pisiferol [ratio **6a** : **6b**(X=$SO_2Ph$) = 1.5:1].

Kametani, Honda and their collaborators[1] have described the synthesis of pisiferol **1** starting with alkylation of the benzocyclobutene **2** with the iodide **3**. Thermolysis of the product **4**(X=H) is believed to proceed *via* the *Z*-*o*-quinodimethane **5**(X=H) which undergoes intramolecular Diels-Alder addition (IMDA) to give the products **6a** and **6b**(X=H) with the pisiferic acid skeleton in 80% yield. Unfortunately **6a**(X=H) with the required *trans*-BC ring junction is the minor product (1 part) and **6b**(X=H) the major product (4 parts). The stereochemical problem was corrected but at the expense of an additional sequence of seven reactions proceeding in 21% overall yield. The IMDA reactions of most *o*-quinodimethanes with a four carbon linking chain between diene and alkene give *trans*-adducts *via exo*-addition of the connecting chain. Since these *o*-quinodimethanes lack a *Z*-cyano group the observed *endo*-chain preference for **5**(X=H) can tentatively be ascribed to repulsion between an *exo*-orientated chain and the *Z*-cyano group. Craig and his collaborators[2] have used the bulky phenylsulfonyl group placed *trans* to the connecting chain as in **7**(X=$SO_2Ph$) to obtain mostly the product of *endo*-chain (*exo*-$SO_2Ph$) addition. In contrast, related systems with X=H give comparable quantities of *cis*- and *trans*- products. Craig suggests the $PhSO_2$ group prefers the less sterically demanding *exo*-position. With this background we argued that in **5**(X=$SO_2Ph$) steric repulsion between the *Z*-cyano group and an *exo*-directed $SO_2Ph$ group might force the $SO_2Ph$ *endo* and the connecting chain *exo* so that the desired *trans*-BC product **6a**(X=$SO_2Ph$) would be favoured. To test this notion **4**(X=H) was cleaved to the aldehyde **8** which gave **4**(X=$SO_2Ph$) by reaction with $PhSO_2CH_2Li$ and elimination of the resulting alcohol (Scheme). Thermolysis of **4**(X=$SO_2Ph$) at 180°C (3h) gave **6a**(X=$SO_2Ph$) and **6b**(X=$SO_2Ph$) in a much improved *trans*:*cis* ratio of 1.5:1 and in 67% yield. In addition to desired adducts the thermolysis provided the *E*,*E*-diene **9**(Y=CN, X=$SO_2Ph$) (*ca* 23%). Although not reported by the earlier workers[1], a similar quantity of **9**(Y=*E*-CN, X=H) is formed in the thermolysis of **4**(X=H). These products arise *via* 1,5-sigmatropic hydrogen shift in an *E*-*o*-quinodimethane intermediate as shown by the arrows in **10**. The size and π-electron accepting ability of the cyano group favour its inward conrotation[3] in competition with an alkyl chain. However the




**Scheme**

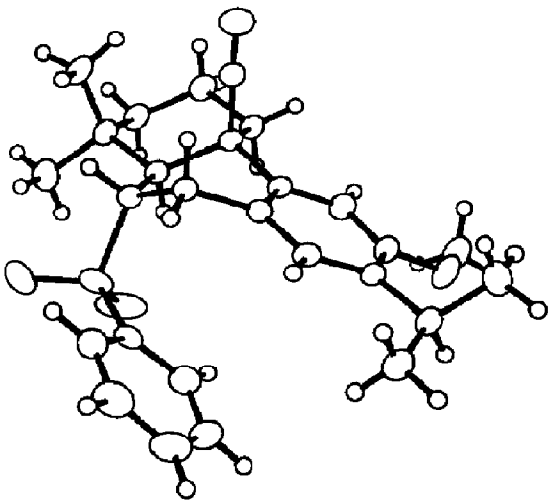
Reagents: i) NaH/DMF, 65°C, 0.5h; ii) $OsO_4$/THF/$H_2O$/$NaIO_4$, 20°C, 7h; iii) $PhSO_2Me$/BuLi/THF, -78°C, 1h; iv) $MeSO_2Cl$/$Et_3N$/THF, -5°C, 14h; v) o-DCB, 180°C, 3h.

benzocyclobutene ring-opening will be reversible unless the 1,5-shift and IMDA reaction are fast. In the event of such reversibility the ratio of products will depend less on the torquoselectitity of ring-opening[4] as on the relative rates of 1,5-shift and IMDA reaction. The situation is therefore finely balanced and represents a potentially serious flaw in the use of benzocyclobutenes as sources of *o*-quinodimethanes for IMDA reactions[5].

Allocation of stereochemistry to **6a** and **6b**(X=$SO_2$Ph) was made on the basis of a very shielded methyl resonance (δ -0.26) in the n.m.r. spectrum of **6b** absent for **6a**[6]. The spectra of both isomers disclose vicinal couplings for the ring-B protons suggesting both compounds prefer to exist with ring-B in a half-boat conformation; the boat structure for **6a** is confirmed by an X-ray structure determination[7] (Fig.). Existence of **6a** in the boat-like conformation shown below is understandable as in the alternative half-chair conformation the $PhSO_2$ and nearby α-Me are much closer. For the half-chair conformation corresponding to **6b** the $PhSO_2$ and CN groups are 1,3-diaxial.

To complete the synthesis of pisiferol the sulphone **6a**(X=$SO_2$Ph) was heated in diazabicycloundecene at 130°C (3h) to give the alkene **11** (92% yield). Hydrogenation of **11** over Pd/C gave **6a**(X=H) (*ca* 98% yield) convertible into pisiferol by reduction, first by di-isobutylaluminium hydride and then with sodium borohydride followed by sodium ethanethiolate-mediated demethylation of the aryl ether[1].

The improvement in the *trans:cis* adduct ratio and the pisiferol synthesis observed here raise interesting possibilities of similar control of the Diels-Alder reactions of other dienes with *Z*-substituents, including 1,4-bridged dienes *e.g.* cyclopentadiene, cyclohexadiene, α-pyrone and furan. We have already shown the effect is important for the 2-benzopyran-3-one **12**. The use of more bulky arylsulfonyl groups may be of value in extending these studies.



**Figure**

**Acknowledgements.**

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**References and notes.**

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3. Niwayama, S.; Houk, K.N. *Tetrahedron Lett.*, **1993**, *34*, 1251. Piers, E.; Ellis, K.A. *ibid.*, **1993**, *34*, 1875; references cited by these authors. Unlike the CHO group $CO_2Et$ generally prefers outward conrotation in competition with hydrogen (but compare Shishido, K.; Shitara, E.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.*, **1985**, *107*, 5810, and Jefford, C.W.; Bernardinelli, G.; Wang, Y.; Spellmeyer, A. B.; Houk, K.N. *J. Am. Chem. Soc.*, **1992**, *114*, 1157).

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5. Attempts to use the larger $CO_2Me$ group in place of CN in **4**(X=$SO_2Ph$) to increase the *trans:cis* adduct ratio failed; thermolysis gave mostly the 1,5-shift products *Z*- and *E*-**9**(Y=$CO_2Me$; X=$SO_2Ph$). Replacement of CN by the larger $CO_2Me$ could lead to more *E*-*o*-quinodimethane **9** and/or slower IMDA reaction within a *Z*-*o*-quinodimethane **5** with $CO_2Me$ replacing CN.

6. Selected spectroscopic data:
**6a**(X=$SO_2Ph$); δ(300 MHz, $CDCl_3$) 1.15 (3H, d, J=6.9, CH$\underline{Me}_2$), 1.23 (3H, s, Me), 1.25 (3H, d, J=6.9, CH$\underline{Me}_2$), 1.36 (3H, s, Me), 1.50 (1H, m), 1.70-2.00 (3H, m), 2.15 (1H, m), 2.22 (1H, d, J=5.0, C$\underline{H}$CHS$O_2$Ph), 2.71 (1H, m), 2.97 (1H, d, J=16.5, benzylic-H), 3.27 (1H, sept, J=6.9, C$\underline{H}$Me$_2$), 3.51 (1H, dd, J=16.5 and 6.0, benzylic-H), 3.77 (1H, t, J=5.5, C$\underline{H}$S$O_2$Ph), 3.81 (3H, s, OMe), 6.63 (1H, s, Ar-H), 6.71 (1H, s, Ar-H), 7.48 (2H, m, $SO_2$Ph), 7.62 (3H, m, $SO_2$Ph).
**6b**(X=$SO_2Ph$); δ(400MHz, $C_6D_6$) -0.26 (3H, s, Me), 1.05 (1H, m), 1.10 (2H, m), 1.12 (3H, s, Me), 1.13 (3H, d, J=7.0, CH$\underline{Me}_2$), 1.17 (3H, d, J=7.0, CH$\underline{Me}_2$), 1.36 (1H, m), 1.77 (1H, td, J=14.0 and 4.0), 2.52 (1H, bd, J=15.0), 2.71 (1H, dd, J=15.0 and 12.0, benzylic-H), 3.11 (1H, d, J=3.0, C$\underline{H}$CHS$O_2$Ph), 3.23 (3H, s, OMe), 3.37 (2H, m, C$\underline{H}$Me$_2$ and C$\underline{H}$S$O_2$Ph), 3.72 (1H, dd, J=15.0 and 7.0, benzylic-H), 6.54 (1H, s, Ar-H), 6.67 (1H, s, Ar-H), 7.00 (3H, m, $SO_2$Ph), 7.97 (2H, m, $SO_2$Ph).
**9**(X=$SO_2Ph$, Y=CN); δ(300MHz, $CDCl_3$) 1.15 (6H, s, 2xMe), 1.20 (6H, d, J=7.0, CH$\underline{Me}_2$), 1.63 (2H, m), 2.31 (3H, s, Ar-$\underline{Me}$), 2.43 (2H, m), 3.28 (1H, sept, J=6.9, C$\underline{H}$Me$_2$), 3.81 (3H, s, OMe), 6.28 (1H, d, J=15.4, olefinic-H), 6.35 (1H, t, J=7.7, C$\underline{H}$C$H_2$), 6.63 (1H, s, Ar-H), 6.98 (1H, d, J=15.2, olefinic-H), 7.01 (1H, s, Ar-H), 7.56 (3H, m, $SO_2$Ph), 7.89 (2H, m, $SO_2$Ph).
**11**; δ(400MHz, $CDCl_3$) 1.03 (3H, s, Me), 1.19 (3H, d, J=7.0, CH$\underline{Me}_2$), 1.21 (3H, d, J=7.0, CH$\underline{Me}_2$), 1.28 (3H, s, Me), 1.58 (1H, m), 1.63 (1H, m), 1.75 (1H, dt, J=13.5 and 3.5), 1.86 (1H, dq, J=14.0 and 3.5), 2.01 (1H, tt, J=14.0 and 3.5), 2.09 (1H, t, J=3.0, *endo*-methine), 2.73 (1H, m), 3.28 (1H, sept, J=7.0, C$\underline{H}$Me$_2$), 3.85 (3H, s, OMe), 6.00 (1H, dd, J=10.0 and 2.5, olefinic-H), 6.66 (1H, dd, J=10.0 and 3.0, olefinic-H), 6.80 (1H, s, Ar-H), 7.01 (1H, s, Ar-H).
**6a**(X=H); δ(400MHz, $CDCl_3$) 1.01 (3H, s, Me), 1.16 (3H, s, Me), 1.18 (3H, d, J=7.0, CH$\underline{Me}_2$), 1.19 (3H, d, J=7.0, CH$\underline{Me}_2$), 1.26 (1H, td, J=14.0 and 3.5), 1.37 (1H, dd, J=12.0 and 2.0, *endo*-methine), 1.52 (1H, td, J=13.5 and 3.5), 1.59 (1H, m), 1.83 (2H, m, C$\underline{H}_2$CH masked by ring C C$\underline{H}_2$), 2.04 (2H, m, C$\underline{H}_2$CH masked by ring C C$\underline{H}_2$), 2.80 (2H, m, benzylic-H masked by ring C C$\underline{H}_2$), 2.94 (1H, ddd, J=16.5, 6.0 and 1.5, benzylic-H), 3.24 (1H, sept, J= 7.0, C$\underline{H}$Me$_2$), 3.81 (3H, s, OMe), 6.83 (1H, s, Ar-H), 6.92 (1H, s, Ar-H).

7. X-ray crystal structure determination of **6a**(X=$SO_2Ph$); $P2_1/n$, $a$ = 11.4371(4), $b$ = 11.9137(4), $c$ = 17.7373(6)Å, $\beta$ = 103.590(3)°, $V$ = 2349.19(14)Å$^3$, $Z$ = 4, $R_1$ = 0.0487, $wR_2$ = 0.1298. Details of the structure have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge, England.

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