π-Facial Diastereoselectivity in the Electrophilic and Electrophilic–Nucleophilic Additions to Dimethyl (1*R*,2*R*,3*S*,4*S*)-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylate

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The π-facial selectivity of attack of electrophilic species (OsO_4, *m*-$ClC_6H_4CO_3H$, BH_3) on the sterically unbiased dimethyl (1*R*,2*R*,3*S*,4*S*)-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylate is controlled *syn* to the *exo* electron-withdrawing ester substituents, and the reactions of phenylselenyl chloride and phenylsulfenyl chloride show opposing diastereoselectivities, which can be explained using the Cieplak transition state theory.

In the debate about the electronic factors controlling the π-facial diastereoselectivity of attack at a trigonal carbon centre[1] much discussion has centred around the prediction of the Cieplak transition state model[2] that both electrophiles and nucleophiles should show the same facial selectivity when attacking equivalently controlled centres. This prediction arises from the assumption that all incipient bonds are inherently electron deficient, and therefore, irrespective of which reacting partner contributes the bonding electrons, the transition state is stabilised by a hyperconjugative interaction between an antiperiplanar electron rich σ-bond and the σ*-orbital of the incipient bond.

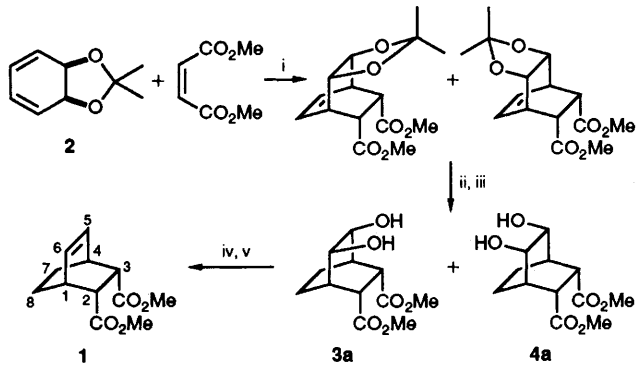
Both le Noble[3] and Mehta[4] have used sterically unbiased structures to test this theory but to date only a few examples of electrophilic additions have been reported. These electrophilic additions have been limited to reactions such as epoxidation and hydroboration because of the exocyclic nature of the double bonds.[5] High selectivities were observed in the oxymercuriation and hydrochlorination reactions; however in these reactions the electrophile adds to the terminus of the double bond and the selectivity observed is that of a nucleophilic addition to an intermediate cation.

Clearly it would be desirable to study a system in which both electrophiles and nucleophiles can attack equivalently controlled centres within one molecule. Presented in this communication are some preliminary results of the addition of electrophilic and electrophilic–nucleophilic reagents to one such system, the sterically unbiased dimethyl (1*R*,2*R*,3*S*,4*S*)-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylate **1**.[6]†

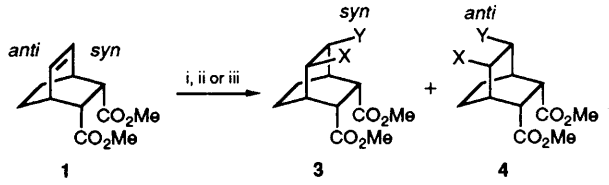
† The numbering system shown in Scheme 1 has been retained throughout the discussion even though it is inconsistent with systematic nomenclature in certain cases.

The *exo* configuration of the ester substituents was controlled by the *endo* stereoselective Diels–Alder reaction between the protected cyclohexadiene-diol **2**[7] and dimethyl maleate, the diastereoisomeric products of which were separated and converted to the diastereoisomeric diols **3a** and **4a** (Scheme 1). Elimination using Samuelssons' conditions[8] gave the desired bicyclo[2.2.2]octene **1** in good yield, the olefinic protons (5-H, 6-H) of which appeared as a double doublet: a ^3J coupling to the adjacent bridgehead proton (5-H–4-H, 6-H–1-H), and a W ^4J coupling to the other bridgehead proton (5-H–1-H, 6-H–4-H).‡

‡ This was prepared using a method of Samuelsson.[8] Chlorodiphenylphosphine (0.44 cm^3, 2.16 mmol) was added to a stirred solution of the diol **3a** (0.28 g, 1.08 mmol) and imidazole (0.292 g, 4.32 mmol) in toluene at 80 °C under argon. After 10 min iodine (0.54 g, 2.16 mmol) was added to the mixture portionwise, and then the mixture was refluxed for 2 h. The mixture was cooled to room temperature, zinc powder (0.65 g, 10.8 mmol) was added and the mixture returned to reflux. After 1 h the mixture was cooled, filtered through Celite and washed with hydrochloric acid (3 mol dm^{-3}) and ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate. The organic layers were combined, washed with aqueous sodium hydroxide solution, water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed (SiO_2, 6:1 light petroleum–diethyl ether) to give the bicyclo[2.2.2]oct-2-ene **1** as an oil (0.249 g, 94%) that crystallised in the freezer but melted at room temperature; ν_{max}/cm^{-1} ($CHCl_3$) 1735 (C=O); δ_H (250 MHz; $CDCl_3$) 6.35 (2 H, dd, *J* 3.2 and 4.8 Hz, 5- and 6-H), 3.66 (6 H, s, 2 CO_2Me), 2.86–2.82 (2 H, m, 1- and 4-H), 2.70 (2 H, s, 2- and 3-H), 1.94–1.90 (2 H, m, J_{gem} 8.5 Hz, *exo*-7-H and *exo*-8-H), and 1.18–1.12 (2 H, J_{gem} 8.5 Hz, *endo*-7-H and *endo*-8-H); δ_C (103 MHz; $CDCl_3$) 173.69, 134.75, 51.47, 43.65, 31.84 and 20.22; elemental analyses were satisfactory.



Scheme 1 *Reagents and conditions*: i, benzene, reflux, 5 days; ii, Dowex 50, MeOH, H_2O, 80 °C, 18 h; iii, Pd/C 10%, EtOAc, H_2O, H_2, 16 h; iv, Ph_2PCl, I_2, imidazole, toluene, reflux, 2 h; v, Zn, reflux, 1 h

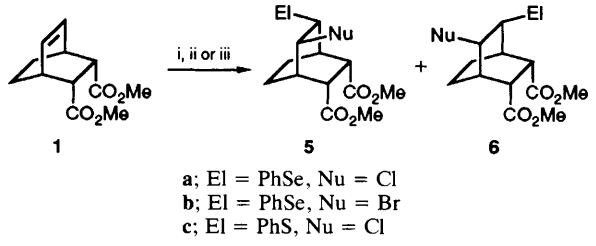


a; X = Y = OH
b; XY = –O–
c; X = OH, Y = H

Scheme 2 *Reagents and conditions*: i, OsO_4, Et_3NO, acetone–water (6:1), 0 °C, 3 h; ii, *m*CPBA, CH_2Cl_2, room temp., 10 h; iii, BH_3, Et_2O, room temp., 3 h, then $NaBO_3$, H_2O, 10 h

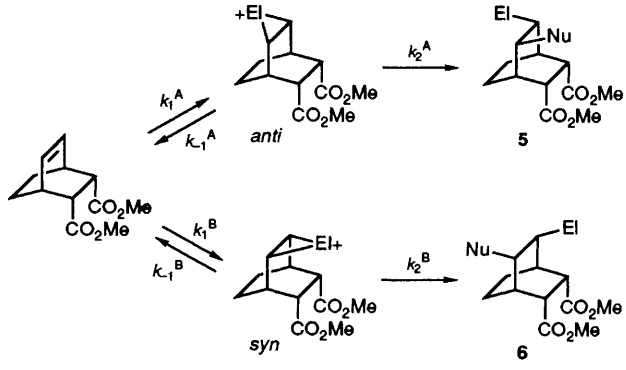
cis-Dihydroxylation of the double bond using catalytic osmium tetroxide conditions gave a mixture of the diols **3a** and **4a** (Scheme 2), which by integration of the crude ^1H NMR spectra were in the ratio of 73:27 *syn* to *anti*. Similarly, epoxidation with *m*-chloroperbenzoic acid (*m*CPBA) cleanly gave an 83:17 mixture of the two epoxides **3b** and **4b** and hydroboration gave the diastereoisomeric alcohols **3c** and **4c** in the ratio of 60:40. In all cases the major *syn* products were identified by their greater deshielding of 2-H and 3-H in the crude ^1H NMR spectra. This *syn* selectivity is consistent with the predictions of the Cieplak model, the vicinal C-1–C-8 and C-4–C-7 bonds being more electron rich than the corresponding C-1–C-2 and C-4–C-3 bonds by virtue of the electron withdrawing ester substituents.

The ^1H NMR spectrum of the crude reaction mixture from the addition of phenylselenyl chloride showed only one major diastereoisomer **5a**, in which the selenium was *anti* to the *exo* ester substituents and the chloride *syn* (Scheme 3). The structure was deduced from the ^1H NMR spectra; the relatively small 5-H–6-H *trans* coupling constant (5.0 Hz) established the *anti* relationship between the selenium and the chloride, and the W coupling between 5-H and *exo*-7-H (2.6 Hz) suggested that the selenium was *anti*. This proposed structure was further confirmed by an NOE experiment which showed a positive enhancement between 5-H and 3-H, and 6-H and *endo*-8-H. Low-temperature ^1H NMR studies showed that the same product was formed at −40 °C and the use of a more polar solvent had no effect on the selectivity of the reaction. Analogously the reaction of phenylselenyl bromide with the olefin exhibited the same diastereoselectivity; however, the product **5b** could be equilibrated at 80 °C in CD_3CN (sealed NMR tube, 50 h), producing a 60:40 mixture of the diatereoisomers **5b** and **6b**, proving that the diastereoisomer **5b** was indeed the product of kinetic control. The diastereoisomer **6b** was easily identified in the ^1H NMR spectra of the mixture by the appearance of a new signal at



a; El = PhSe, Nu = Cl
b; El = PhSe, Nu = Br
c; El = PhS, Nu = Cl

Scheme 3 *Reagents and conditions*: i, PhSeCl, $CDCl_3$ or CD_3CN, room temp.; ii, PhSeBr, $CDCl_3$ or CD_3CN, room temp.; iii, PhSCl, $CDCl_3$ or CD_2Cl_2, 0 or −78 °C



Scheme 4

δ 4.28 corresponding to 6-H which contained an additional W coupling (2.0 Hz) to *exo*-8-H.

However, the reaction of phenylsulfenyl chloride[9] (0 °C, $CDCl_3$ or −78 °C, CD_2Cl_2) gave a mixture of the diastereoisomers **5c** and **6c** in the ratio of 37:63 from integration of the 5-H signals (δ 4.03 and 3.89), the major isomer being that in which the sulfur was *syn* and the chloride *anti*.§ Unfortunately it was not possible to separate the diastereoisomers **5c** and **6c**, and therefore identification was made by comparison of the crude spectrum with those of the pure diastereoisomer **5a** and the mixture of **5b** and **6b**.

The difference in the selectivity of the reaction of the phenylselenyl and sulfenyl halides can be explained by a change in the rate determining step.[10] Clearly in the reaction of phenylsulfenyl chloride, k_2^A and k_2^B (Scheme 4) are greater than k_{-1}^A and k_{-1}^B respectively (electrophilic addition is the rate determining step), and the selectivity observed is that of electrophilic addition to the double bond. However, in the reaction of phenylselenyl chloride, k_{-1}^A and k_{-1}^B must be greater than k_2^A and k_2^B, and therefore the formation of the diastereoisomeric intermediates becomes reversible (nucleophilic attack is the rate determining step), the selectivity in the product arising from the difference in k_2^A and k_2^B. Since approach of the attacking species *syn* to the ester substituents is favoured, then the nucleophiles preferentially reacts with the *anti* episelenium ion, *i.e.* k_2^A is greater than k_2^B. The relative ease with which the phenylselenyl bromide adduct **5b** undergoes equilibration to the diastereoisomer **6b**, *via* dissociation back to the olefin, suggests that the difference between k_2^A and k_2^B is only small.

This study has shown that soft electrophiles and hard nucleophiles show π-facial diastereoselectivity consistent with the Cieplak transition state model, and that this disubstituted

§ As noted by one of the referees we have not proved that the ratio of sulfenylation is that which is formed under kinetic control. All attempts to equilibrate this mixture at high temperature failed, with no change in the product ratio being observed at temperatures under the critical temperature of the solvent ($CDCl_3$). However, we believe that under the low-temperature conditions of the reaction it would be very surprising if the thermodynamic products were formed.

bicyclo[2.2.2]octene is a useful tool with which to probe these type of addition reactions. Investigations into the additions of hard electrophiles at remotely controlled trigonal carbon centres are currently underway in this laboratory.

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