Complete Stereoselectivity in the Intramolecular Diels–Alder Reaction of an Ester derived from 'Diacetone Glucose'

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The intramolecular Diels–Alder reaction of the ester (**3**), which is readily obtainable from 'diacetone glucose,' gives compound (**4**) but under the reaction conditions substantial 1,3-prototropic shift occurs with the formation of (**8**).

Previous results from our laboratory have shown that carbohydrate-derived α-enones[1] and conjugated dienes[2] undergo Diels–Alder reactions with extremely high efficiencies and stereoselectivities.[3] Of particular interest is the reaction of maleic anhydride with the readily prepared diene (**1a**)[2,3] which was totally stereoselective: the addition was (a) on the face opposite to the acetonide ring, and (b) in the *endo* mode. Intramolecular Diels–Alder reactions have been shown to be remarkably efficient for the simultaneous assembly of several stereocentres.[4] Such a process employing the diene (**1**) therefore seemed worthy of exploration, particularly since there is only one study of which we are aware in which chirality resides on the diene moiety of an intramolecular Diels–Alder precursor.[5]

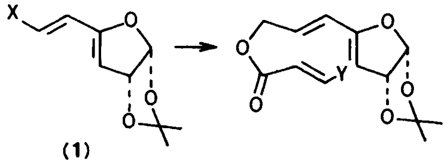
The first substrate examined was the ester (**2**), readily obtained by acylating the previously described[2] dienic alcohol (**1b**) with acryloyl chloride. Heating of (**2**) in toluene caused only decomposition, there being no evidence of a Diels–Alder adduct.

In the expectation that a more electron-deficient dienophile would fare better, we studied the dicarbonyl system (**3**).† We noted that the condensation of maleic anhydride with (**1a**) had occurred entirely opposite to the dioxolane ring,[3] and on that basis, the transition states I and II (Figure 1) were deemed to be the most favourable for (**3**). However, the fact that α-face adducts are disfavoured in the *inter*-molecular reaction of (**1a**) was not considered a sound basis for excluding comparable addition products in the *intra*-molecular reaction, where entropic factors might allow the system to overcome the non-bonded interactions presented by the bulky acetonide. Thus, the α-face transition states III and IV were also thought to be possible.

Figure 1 shows the possible products (**4**)—(**7**) corresponding to the transition states I → IV and the expected values for $J_{2,3}$, based upon our previous studies of annulated furanoses.[3]

In the event, heating of (**3**) in toluene for 3 days gave rise to a complex mixture, the composition of which depended upon the duration and temperature of the reaction. Careful and repeated column chromatography allowed two crystalline products to be separated from minor components in 30 and 10% yields, whose molecular ions were consistent with intramolecular Diels–Alder products. Furthermore, both substances reacted with hydrogen to give crystalline dihydro derivatives.

The ^{1}H n.m.r. spectrum of the major product did not show a vinyl hydrogen, and it was hydrogenated less readily than the comparable adducts from the intermolecular reactions.[3]



(**1**)
a; X = H
b; X = CH$_2$OH

(**2**) Y = H
(**3**) Y = COMe

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† The ester (**3**) was prepared by the reaction of the alcohol (**1b**) with the acid chloride of *trans*-4-oxopent-2-enoic acid. A shorter route to the acid than that previously reported[6] involved a Wittig condensation of glyoxylic acid hydrate with Ph$_3$P=CHCOMe. Full details will be described later.

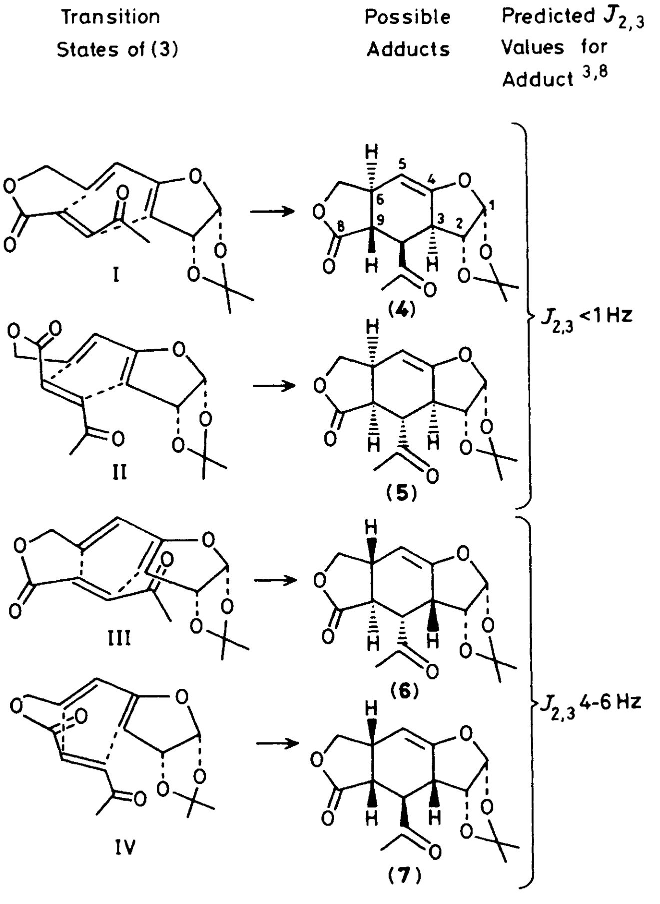
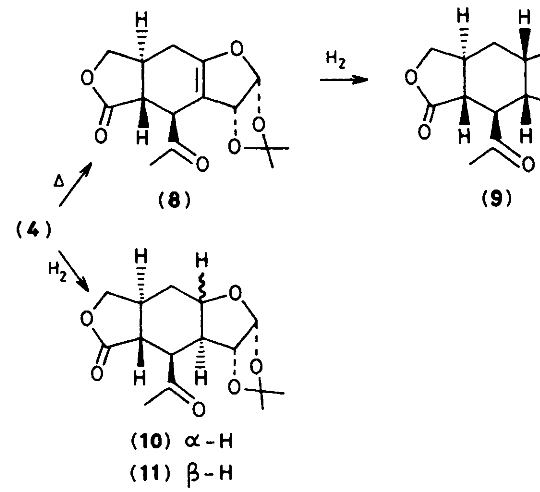


Figure 1



(8) (9) (4) (10) α-H (11) β-H

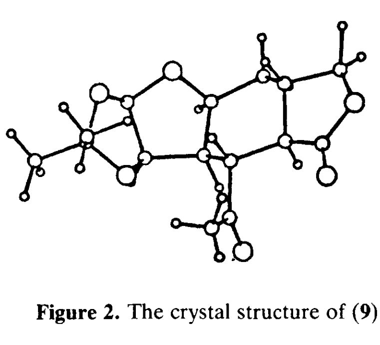


Figure 2. The crystal structure of (9).

However, a crystalline *dihydro* product was obtained which showed a $J_{2,3}$ value of 7.5 Hz, indicating a *cis* relationship between H-2 and H-3 (Figure 1). This result was not consistent with the β-face adduct, (**4**), and we therefore resorted to *X*-ray analysis of the *dihydro* product (**9**) with the result shown in Figure 2.‡ The structure of compound (**9**) suggested that the major product was compound (**8**).

Hydrogenation of the pure, crystalline minor product gave rise to a trace amount (*ca.* 1%) of compound (**8**). Thus, the configurations at C-6, C-9, and C-10 for the minor product were the same as in (**8**). The $J_{2,3}$ value of 1.0 Hz implied a *trans* relationship between H-2 and H-3 (see Figure 1) and the minor product was therefore assigned structure (**4**).

The stereochemistry of the hydrogenation product [(**10**) or (**11**)] was apparent from the $J_{3,4}$ value of 13.1 Hz which implied a *trans*-relationship for H-3 and H-4. Thus the product must be (**11**). The large $J_{2,3}$ value of 6.5 Hz was rationalized by examination of models which showed that the dihedral angle involving H-2 and H-3 is *ca.* 180°.

Upon heating in refluxing toluene, compound (**4**) was converted cleanly into (**8**) thereby establishing that this transformation had occurred under the intramolecular Diels–Alder conditions. The driving force for the rearrangement is probably (a) the fact that a double bond prefers to be 'across from' the ring-junction in *trans*-fused 6/5 systems,[7] and (b) the fact that the double bond in (**8**) is tetra-substituted.

These results show that systems related to, or derivable from, diene (**1**) undergo both inter- and intra-molecular Diels–Alder condensations with excellent, if not complete, stereoselectivities. Thus, this reaction occurs from the anti-β-face transition state I (Figure 1). This conclusion seems justified since no products clearly related to (**5**), (**6**), or (**7**) were isolated even in 1% yields.

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‡ Crystals of the dihydro product (**9**) are orthorhombic, space group $P2_12_12_1$ with a = 5.376(1), b = 11.633(2), c = 24.195(4) Å, U = 1513.1(4) Å^3, Z = 4, D_c = 1.301 g cm^{-3}, $F(000)$ = 632, λ = 0.71069 Å, $\mu(\text{Mo-}K_\alpha)$ = 1.083 cm^{-1}. Intensity data were collected on a crystal of dimensions 0.4 × 0.4 × 0.5 mm using θ–2θ scans ($3.2 < 2\theta \leqslant 55.0°$) on a Syntex P2$_1$ diffractometer. From a total of 2049 measured reflections, 1300 with $I \geqslant 3\sigma(I)$ were considered observed and used in the structure solution and refinement. The structure was solved by direct methods (MULTAN 80) and refined with anisotropic thermal parameters by full-matrix least-squares methods to an R of 0.085. At this stage all hydrogen atoms were located from a difference Fourier map and included in the refinement which converged at R = 0.036 and R_w = 0.038 $\{R_w = [\Sigma w(|F_o|-|F_c|)^2/\Sigma w|F_o|^2]^{1/2}$, w^{-1} = 2.76 − $0.088|F_o|$ + $0.0042|F_o|^2\}$. A final difference map was featureless with maximum residuals of 0.22 e Å^{-3}. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.